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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Pikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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STREPTOMYCIN: SOME HISTORICAL ASPECTS OF ITS DEVELOPMENT AS A CHEMOTHERAPEUTIC AGENT IN TUBERCULOSIS[1]

WILLIAM H. FELDMAN[2]

When Dr. Towey invited me to relate some of the historical aspects of the development of the use of streptomycin in tuberculosis, my first reaction to his suggestion was that everything worth hearing about this drug had already been said, and said repeatedly. It occurred to me that the printing press, the loud speaker, and the TV screen had covered the subject completely; so completely, in fact, that it seemed incredible that there could exist anyone, least of all in this audience, who hadn't heard and who didn't know all about the "conception," "birth," and "extra-uterine development" of this substance.

As we explored the subject conversationally, it developed that what Dr. Towey had in mind was a somewhat informal account of my personal experiences, particularly as they were related to the question of how Dr. H. Corwin Hinshaw and I had the good fortune to obtain streptomycin for testing its antituberculous potentialities at a time when only a relatively few grams of the material existed.

What I have prepared is by no means a definitive account of the streptomycin-tuberculosis story. Rather, it represents, in a more or less chronologic sequence, a somewhat sketchy but factual recounting of events during a ten-year period which culminated in the general acceptance of the fact that clinical tuberculosis is definitely amenable to chemical therapeutics.

Much that might be of interest has been omitted and some of what is included may seem irrelevant and trite. I have revised the manuscript several times, striving to keep the presentation safely within the physiologic limits of the endurance of my listeners. If despite my concern for your welfare your mind wanders, if you have an irresistable desire to sleep, and if you experience frighten-

[1] Dr. Feldman received the Dearholt Medal for outstanding contributions to tuberculosis control at the Mississippi Valley Tuberculosis Conference, October 15 to 17, 1953. As part of the award ceremonies, Dr. Feldman was requested to relate his personal experiences in the development of streptomycin. At the importuning of the REVIEW, Dr. Feldman has reluctantly but graciously given his consent to the publication of his remarks on that occasion.—*The Editor.*

[2] Mayo Clinic and Mayo Foundation, Rochester, Minnesota. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

ing apprehensions of impending doom, do not despair; there *is* a doctor in the house.

GENERAL BACKGROUND

The story of the relation of my former associates, Drs. H. Corwin Hinshaw and Karl Pfuetze, and myself to streptomycin as a tuberculosis antagonist began several years before the discovery of this drug. In the late nineteen thirties a new era of chemotherapy of infectious diseases had begun with the discovery of the antimicrobial action of the sulfonamides. The drugs of the sulfonamide series revolutionized the treatment of the forms of acute respiratory infections due to gram-positive bacteria. That these and many other sulfonamide drugs should be tried in tuberculosis was inevitable.

In 1939, after it had been reported that sulfanilamide had a limited suppressive effect in experimental tuberculosis in guinea pigs (1), Dr. H. Corwin Hinshaw, my collaborator for many years at the Mayo Clinic, drew my attention to the work in England with sulfapyridine in the treatment of pneumonia. He suggested that, since observations with sulfanilamide indicated some deterrent effects against the tubercle bacillus *in vivo*, we might explore the possibilities of sulfapyridine against a similar infection. This we did. Our results were generally comparable to what Rich and Follis had observed previously with sulfanilamide. This was our first attempt to suppress a tuberculous infection by the use of a drug. Subsequently, we tried *in vivo* practically all of the more commonly used sulfonamide compounds as well as many others which were never exploited commercially. The results revealed the limited effectiveness and the potential toxicity of this group of chemicals. These factors we considered prejudicial to their use in clinical tuberculosis. Additional work with this class of compounds did not seem justified.

In 1940, Dr. Hinshaw, as a consequence of a conference in Detroit with Dr. Elwood A. Sharp, learned of a sulfone compound designated Promin. This substance had been synthesized in the Research Laboratories of Parke, Davis & Company, of which Dr. Sharp was and is Director of Clinical Investigation. At the time, Promin was being subjected to extensive clinical trials in a considerable variety of bacterial diseases, but not including tuberculosis.

Dr. Hinshaw indicated his interest in Promin for clinical investigation, and Dr. Sharp offered to make a supply available, presumably for clinical trials in pneumonia. However, by the time the drug was received in Rochester, Dr. Hinshaw and I had formulated plans to divert a portion of the supply to an animal experiment to determine what effect, if any, Promin might have as an antituberculous agent. The experiment was started in May, 1940, and terminated approximately five and one-half months later. The results revealed that Promin had exerted a notable inhibition on the course of a human-type tuberculous infection in guinea pigs, animals highly susceptible to this form of tuberculous infection.

The favorable results of the first experiment with Promin, which were published in October, 1940, were exciting and could not be ignored (2). They served

to intensify our intentions to proceed with our investigations. We were certain that tuberculosis was vulnerable to successful chemotherapy. Consequently, we undertook what eventually proved to be an extensive study of Promin and many related sulfones, including Promizole, in experimental as well as in clinical tuberculosis (3).

The results of these many studies, which continued for a period of several years, indicated unequivocally that certain of the sulfone compounds were highly effective in well-established progressive experimental tuberculosis in guinea pigs. Thus, despite the skepticism of many, we were able to challenge successfully the concept that tuberculosis was not susceptible to attack by specific drug therapy.

That we had been able to demonstrate the vulnerability of the pathogenesis of tuberculosis to the action of a specific chemical substance was gratifying and of significance in sustaining our enthusiasm and persistence in the search for more effective agents. We had in a sense "got our foot in the door," a door which previously had seemed an impassable obstacle. However, the shortcomings of Promin in clinical trials indicated that our triumph was incomplete and that the search for drugs more effective than this sulfone was just beginning.

Promin is of much significance historically. This compound was the first antimicrobial substance which was proved unequivocally effective in suppressing an experimental tuberculous infection induced by the human-type tubercle bacillus. Furthermore, the observation that Promin was an effective antagonist against experimental tuberculosis was soon followed by the use of this drug at Carville, Louisiana, in the treatment of another mycobacterial disease, leprosy. Subsequently, the extensive use in leprosy of Promin and of other related sulfones throughout the world had a tremendous impact on the social and medical aspects of this disease. They have for several years been considered the treatment of choice.

During the earlier phases of our attempts to find an effective substance which would be useful in the treatment of the tuberculous patient, much attention was given to the development of what we believed to be scientifically sound experimental procedures. Eventually, methods evolved which were for our purpose relatively precise and which yielded results that were repeatable and information on which the clinical possibilities of a new drug might be predicted. Consequently, when we had the opportunity to study streptomycin *in vivo* against experimental tuberculous infections, reliable laboratory procedures were immediately available and the results could be accepted with confidence.

STREPTOMYCIN

Until 1944 we had not tried any of the relatively few antibiotics available during this period. The drugs we had tested were synthetic organic compounds. In 1943, we turned our attention to the possibility of obtaining for *in vivo* study against tubercle bacilli any likely antibiotic which was not unduly toxic.

We were aware of the eminence of Dr. Selman A. Waksman of Rutgers University, New Brunswick, New Jersey, in the field of microbiology of soil and

were impressed by the issuance from his laboratory from time to time of reports on new antibiotic substances.

In July, 1943, I wrote to Dr. Waksman inquiring if clavacin, a highly potent antibiotic he and his associates had recently discovered, might be available, and expressed my desire to visit his laboratory. Dr. Waksman replied that, owing to its high toxicity, clavacin had proved disappointing. He closed his letter by graciously indicating that he would be glad to have me visit him at any time which was convenient.

An opportunity to visit Dr. Waksman did not develop until some months later. Finally in November, 1943, I was able to go to New Brunswick, where I met Dr. Waksman by appointment on November 16. On this occasion I recounted the results of the work Dr. Hinshaw and I had been doing in our search for a safe and useful drug in the treatment of tuberculosis. In turn, Dr. Waksman mentioned briefly the *in vitro* work under way in his laboratory in seeking microbes which might have an effective antagonism against tubercle bacilli.

I expressed our interest in any new substance which might be discovered and assured him we would be in a position to do experiments with animals if he should obtain a substance which he believed worthy of *in vivo* trial against *M. tuberculosis*.

After leaving Dr. Waksman's office, he conducted me through his research laboratories, where I had the pleasure of being introduced to Dr. Albert Schatz, who at that time was associated with Dr. Waksman as a graduate student. As a co-discoverer of streptomycin, Dr. Schatz eventually attained fame and eminence.

Three weeks after my visit, Dr. Waksman wrote that he would keep me informed concerning the progress of their work and, should an agent be obtained that appeared to be worthy of *in vivo* tests against the tubercle bacillus, we would receive a supply for experimental study.

A few weeks later, in January, 1944, the discovery of streptomycin was announced in a publication by Schatz, Bugie, and Waksman (4). Among the many organisms listed in tabular form as being susceptible *in vitro* to the antagonistic action of streptomycin was *Mycobacterium tuberculosis*, but whether or not the strain tested was a virulent or an avirulent laboratory stock strain was not indicated.

Dr. Hinshaw and I read the report announcing the discovery of streptomycin and were eager to obtain sufficient material to test its performance in experimental tuberculosis. A request to Dr. Waksman was contemplated when, on March 1, 1944, presumably having in mind an *in vivo* study of the new substance such as I had mentioned previously, he wrote to inquire if we were prepared to undertake such a test (5).

After a further exchange of correspondence, I requested 10 gm. of the material, which from the meager knowledge available we estimated would be sufficient to test its antituberculous activity in a small number of infected animals.

This material was received from Dr. Waksman during the first part of April, 1944, and, on April 27, our first experiment with streptomycin, consisting of

only 4 guinea pigs, was started. Owing to the exhaustion of our supply of streptomycin, the experiment was terminated on June 20, 1944, fifty-four days after the animals had been infected. The results suggested that, despite its many impurities, this new substance was well tolerated at a therapeutic level sufficient to exert a marked suppressive effect on otherwise irreversible tuberculous infection in guinea pigs. However, despite the marked suppressive effect on the pathogenesis of the infection, it was recorded that streptomycin had not destroyed all of the tubercle bacilli in the tissues of the treated animals and that, therefore, under the conditions imposed, the action of the drug was essentially bacteriostatic rather than bactericidal. This observation was confirmed later in the clinical application of the drug.

We concluded that the results of our first experiment were sufficiently impressive to warrant additional experiments to determine if our initial observations could be confirmed (6).

Whether or not streptomycin for additional *in vivo* experiments would be available was uncertain. The nation was concerned with the demands of a war economy to which the manufacturers of pharmaceuticals were committed, practically to capacity. Furthermore, the evidence in support of further demands for streptomycin, in quantities we required, was rather unsubstantial, consisting of the results with only 4 guinea pigs.

We communicated the results of our first experiment to Dr. Waksman and indicated the urgency for a more comprehensive study. He was, of course, much interested in our preliminary observations and agreed that further studies should be undertaken. The important question was: Could the streptomycin needed be obtained?

To pursue the matter more satisfactorily, Dr. Hinshaw and I journeyed to New Brunswick in the early part of July, 1944. We discussed with Dr. Waksman the type of further experimentation we believed would be necessary and gave an estimate of the amount of drug necessary to accomplish the studies we believed should be done.

Parenthetically, I should mention that, as soon as we were aware of the implications of the results of our first (or 4 guinea pigs) experiment, we proceeded, on June 28, 1944, to infect a large group of guinea pigs, with the rather presumptuous expectation that somehow from somewhere additional streptomycin would be forthcoming. In retrospect, we could properly have been considered somewhat impetuous, but subsequent events proved the wisdom of our procedure.

The amount of streptomycin which we would require was greatly in excess of what could be produced in Dr. Waksman's laboratory. Consequently, he had interested Merck & Co., Inc., of Rahway, New Jersey, in the possibility of producing the streptomycin necessary for our needs. It was arranged that we were to meet with representatives of Merck & Co. the following day.

The meeting with Merck & Co. on July 10, 1944, proved an exciting and memorable occasion. We presented our meager evidence in support of our desire to undertake a further investigation of streptomycin, emphasizing the clinical importance should our original observation be confirmed.

After an extensive discussion of the many facets of the problem which our requirements for streptomycin would create in an already overburdened pharmaceutical factory, the Merck representatives agreed to make the streptomycin necessary for our animal experiments provided we would consent to determine at the same time the effectiveness of another antibiotic, streptothricin. This we readily consented to do. Thus, the future and prompt development of streptomycin as a useful medicinal was assured. Had Merck & Co. not consented to do this at this time, the clinical evaluations of streptomycin would in all probability have been long delayed.

To appraise properly the potential antituberculous capacities of streptomycin, we believed that this drug should be subjected to the same type of long-term experiment that we had used successfully in our previous studies of Promin and of Promizole. With this in mind, we planned to delay the beginning of therapy for six to seven weeks after the animals had been infected. After this period of infection and before the beginning of therapy, the liver of each animal in the experiment—controls as well as those to be treated—was to be subjected to biopsy. This was to establish unequivocal evidence of the existence of lesions of tuberculosis before treatment was started and to enable us to compare the situation revealed at biopsy with that present after treatment, when the experiment was terminated. The duration of treatment was to be five to six months. This would provide a type of experiment quite dissimilar to our initial study, which was terminated after fifty-four days.

We also proposed, if sufficient streptomycin could be obtained, to undertake immediately an experiment similar in character to the first, to determine if our initial observations could be confirmed. This was to be an experiment of relatively short duration. It was important for Merck & Co. as well as for us to know as soon as possible if our previous results were repeatable.

It was agreed that this latter study, which was designated *Experiment No. 2*, should also be done. The experiment was started soon after our return to Rochester and was terminated after sixty-one days. The results supplied complete confirmation of the results obtained in our first experiment (6).

THE CRUCIAL EXPERIMENT

As mentioned previously, the animals for the crucial, or third, experiment had been inoculated with virulent tubercle bacilli on June 28, 1944. Forty-nine days later, liver biopsies were done by Dr. F. C. Mann, at that time Director of the Institute of Experimental Medicine, Mayo Foundation. Treatment was started immediately after the surgical procedures and was continued for 166 consecutive days. The experiment was terminated on January 29, 1945.

The results of the long-term experiment were impressively favorable. The findings demonstrated the unquestionable ability of streptomycin to reverse the potentially lethal course of well-established inoculation tuberculosis in guinea pigs, and the relatively low toxicity and corresponding safety of purified streptomycin. These observations, Dr. Hinshaw and I believed, satisfied the prerequisites of a therapeutic substance worthy of trial in clinical tuberculosis (7).

Subsequently several other experiments were done, all of which supplied information on important aspects of the streptomycin-tuberculosis relationship (8).[2]

As a result of these additional investigations, it was established: (*1*) that bovine as well as human tubercle bacilli are sensitive to the action of streptomycin and that the action is not strain-specific; (*2*) that it is not necessary to administer the drug at frequent intervals every few hours to obtain satisfactory therapeutic effects; (*3*) that streptomycin is not effective in suppressing experimental infections due to tubercle bacilli resistant to the drug *in vitro*; and (*4*) that the potency of streptomycin as an antituberculous agent is sufficient to modify favorably and often dramatically the progression of a tuberculous infection even though the animals are inoculated with large amounts of tubercle bacilli intravenously.

These experiments concluded the first phase of our experimental studies of streptomycin as a tuberculosis antagonist.

CLINICAL ASPECTS

Beginning in December, 1944, the production of streptomycin by Merck & Co. had progressed sufficiently to enable Dr. Hinshaw, in collaboration with Dr. Karl H. Pfuetze, then Medical Superintendent of the Mineral Springs Sanatorium, Cannon Falls, Minnesota, and several associates at the Mayo Clinic to begin a series of preliminary observations on the effect of the drug on cases of clinical tuberculosis. In September, 1945, a preliminary report on 34 cases was published (9). In January, 1946, we were able to report on a total of 54 cases of clinical tuberculosis in which the patients had received streptomycin in excess of four weeks (10), and the number of cases had increased to 75 by June of the same year (11).

An important aspect of the first report on the use of streptomycin in clinical tuberculosis was reference to and description of certain toxic effects of the drug of variable significance. These untoward effects included reactions to sensitization and the recognition and interpretation of disturbances of the vestibular apparatus. These latter toxic effects of streptomycin, which apparently had not been observed previously, were ascribed to a selective neurotoxic effect on the eighth cranial nerve (9).

In these earlier reports on the clinical use of streptomycin, it was emphasized that in a disease such as tuberculosis the drug did not exert a rapidly curative effect, although it did appear to modify the course of the disease in a favorable manner and was capable of exerting a suppressive effect on previously progressive types of the disease. It was pointed out that the action of the drug seemed to be largely bacteriostatic and that the usefulness of streptomycin in clinical tuberculosis is apparently dependent on continuation of the suppressive action of the drug for an indefinitely long period (8). To preclude undesirable effects on the public, patients, and physicians, we assiduously avoided an attitude of

[2] In the latter phase of the studies of streptomycin in experimental tuberculosis, I was privileged to have the capable and enthusiastic assistance of my associate, Dr. A. G. Karlson. For his valuable contribution, I am especially grateful.

excessive optimism and expressed the opinion that extensive and prolonged clinical investigation would be required to determine the place of streptomycin in the treatment of clinical tuberculosis. Now, eight years later, many phases of the problem still require additional elucidation.

EARLY STREPTOMYCIN CONFERENCES

By early 1945 the preliminary studies of streptomycin had indicated its future possibilities as a safe and effective medicinal substance, and a considerable number of progressive manufacturers of pharmaceuticals became seriously interested in its development. As production increased, the demands, despite its high cost, greatly exceeded its availability.

However, late in 1944 and early in 1945, the clinical potentialities of streptomycin having been indicated, the production of the drug had reached a sufficient volume to permit its limited distribution for investigative purposes to several individuals and groups. During this period, the Committee of Medical Research of the Office of Scientific Research and Development in Washington, which exercised authority in the distribution and use of medicinals in short supply, arranged a conference of those who had been investigating streptomycin as an antibacterial agent. Dr. Hinshaw and I were invited to attend and present our results with clinical and experimental tuberculosis. The conference was held on June 14, 1945, under the chairmanship of Dr. Chester S. Keefer.

As a consequence of the information presented at the meeting, the importance and future promise of the various projects were appraised, and relative priorities for the further distribution of streptomycin for research purposes were determined. Fortunately, our work with tuberculosis was regarded with favor and a continuing supply of streptomycin for study of its effectiveness in tuberculous infections was assured.

On June 20, 1945, about one week after the meeting in Washington just referred to, a somewhat similar conference was arranged by Merck & Co. at Rahway, New Jersey. Dr. Hinshaw and I were invited to present reports on the effectiveness of streptomycin in tuberculous infections, experimental and clinical.

The management of Merck & Co. must have been impressed by the preliminary reports on the therapeutic performance and future possibilities of the new drug, since shortly thereafter the company assumed the considerable financial risk of authorizing the construction of a new plant at Elkton, Virginia. This was completed in 1946 and has been in production since that time.

The next important event indicative of the increasing interest in streptomycin was the opportunity Dr. Hinshaw and I had to present a summary of our observations at the 42nd annual meeting of the National Tuberculosis Association in Buffalo, New York, June, 1946.

During the discussion that followed our presentations, we were completely surprised and greatly pleased when Dr. Walsh McDermott and Dr. Carl Muschenheim announced that they and their associates at Cornell University Medical College, New York, had confirmed our observations.

That our findings had been confirmed was, of course, highly gratifying to Dr.

Hinshaw and myself and contributed significantly to the prompt acceptance of streptomycin as a potentially useful drug in the chemotherapy of tuberculosis. The subsequent development of antituberculous therapy immediately assumed an accelerated tempo.

The favorable reception of our respective reports at the Buffalo meeting of the National Tuberculosis Association was a heartening experience and was in marked contrast to the skepticism—and I might say the cynicism—with which our reports on Promin had been received at the 38th annual meeting of the same organization, held in Philadelphia four years previously in May, 1942.

On this previous occasion it had been our impression that few in the audience believed what we said, many didn't understand, and some were sure that we were wasting our time in searching for an effective chemotherapeutic agent useful in the medical care of the tuberculous patient.

Time does not permit a recounting of the several important subsequent developments that eventually yielded an impressive amount of pertinent information which established streptomycin as the first effective practical chemotherapeutic substance in the treatment of clinical tuberculosis.

CONCLUSION

Before closing it should be said that the development of streptomycin in the therapeusis of tuberculosis, like the development of other successful chemotherapeutic agents, was not the result of a carefully planned attack based on a knowledge of the vulnerable biochemical factors of the tubercle bacillus either *in vitro* or *in vivo*. Instead, the approach was entirely empirical, based on the assumption that all microbial life is susceptible to antagonistic factors of varying physical and chemical characteristics.

In the absence of sufficient, precise information regarding the intrinsic mechanisms on which microbial life is dependent, it has not been possible in the search for new microbial antagonists to devise, by chemical manipulation, a predictable, effective, nontoxic substance whose performance *in vivo* will meet successfully the exacting requirements of an antimicrobial agent against a specific pathogenic microorganism.

A thorough knowledge of the disease and the application of systematic, reliable, and tedious methods of experimental pathology are prerequisites for the successful search for new antimicrobial substances. However, despite the refinements of methods and the most diligent devotion to the task, the finding of new bacterial antagonists has been dependent largely on chance rather than on science.

It would be highly gratifying intellectually to have it said that our attack on the problem of specific chemotherapy of tuberculosis was based on a comprehensive and astute understanding of the physiologic chemistry of the tubercle bacillus. Unfortunately, such was not the case. Instead our approach was similar to that of countless others: a formula consisting largely of enthusiasm, hope, faith, persistence, and luck. Perhaps the latter was the most important ingredient.

Although modern chemotherapy of tuberculosis has contributed much in

combating this disease, it is well to be reminded that the final conquest of tuberculosis is not yet in sight. Furthermore, there exist valid doubts whether the disease can ever be banished by the use of specific chemotherapeutic substances alone, even by drugs far more potent than any presently foreseeable. We should, nevertheless, experience a sense of gratification that the advent of practical and effective medicinals has become a source of reassurance to the tuberculous patient. Furthermore, it has armed the phthisiologist with new weapons with which he can prescribe with confidence an effective therapeutic regimen for the recovery of the patient and his restoration to a useful and productive life.

To have had a part in this achievement which has revolutionized many archaic concepts of tuberculosis, a disease that is still unconquered and remains a threat to millions, has been richly rewarding. Few, indeed, have had a comparable opportunity, and Dr. Hinshaw and Dr. Pfuetze would wish to join me in saying we are humbly grateful.

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PREOPERATIVE AND POSTOPERATIVE CARDIOPULMONARY FUNCTION STUDIES IN PATIENTS WITH BRONCHIECTASIS[1, 2, 3]

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INTRODUCTION

The management of bronchiectasis, one of the most common of all chronic pulmonary disorders, frequently presents a problem. Until comparatively recent years, excisional surgery offered the only worthwhile treatment for the patient with significant bronchiectatic involvement. Furthermore, the disease carried a high eventual mortality rate. It appears quite probable, however, that the introduction of potent antimicrobials has resulted in a significant alteration of this situation. A number of observers (1–3) have noted a progressive decline in the number of patients seen with the severe and widespread type of bronchiectasis which formerly accounted for the high death rate in patients with this disease. This can be attributed to more effective prevention and medical management of those infections, such as bronchopneumonia, which are the common precursors of bronchiectasis (4). In addition, there is no doubt that the development of the newer antimicrobial agents has made it possible to pursue a program of medical management which offers better prospects of effective control of the disease than could be anticipated until a few years ago. The resection of bronchiectatic segments of lung, while presenting good prospects of a satisfying clinical result, is not necessarily an unmixed blessing. The risk of a significant impairment in cardiopulmonary function consequent to excisional surgery (5–9) must be added to that inherent in the operation.

These considerations suggest the necessity of re-evaluating the problem of managing the bronchiectatic patient. In weighing the factors for and against surgical treatment, an assessment of the patient's functional status assumes a role of major importance. It is necessary to know the effect on function resulting from the pathologic process and to be able to predict with reasonable accuracy the further changes which may be expected to follow operation. It was in an attempt to clarify these points that the present study was undertaken.

PLAN OF INVESTIGATION

Materials

The present investigation is based on data from a group of 64 patients with bronchiectasis treated at the U. S. Naval Hospital, St. Albans, New York,

[1] From the Cardiopulmonary Function Laboratory, U. S. Naval Hospital, St. Albans, New York.

[2] These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and the State University of New York, NR 115012.

[3] Presented, in part, before the Medical Session, as part of the session on *Surgery in the Treatment of Pulmonary Diseases*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 21, 1953.

TABLE 1A

PHYSICAL CHARACTERISTICS AND CLINICAL DATA OF 38 PATIENTS WITH UNILATERAL BRONCHIECTASIS

LABORATORY NUMBER	AGE (YEARS)	SEX	HEIGHT (CM.)	WEIGHT (LBS.)	BODY SURFACE AREA (m^2)	NUMBER AND LOCATION OF SEGMENTS*		REMARKS†
						Diseased	Resected	
2-Segment Group								
0384	59	M	173	156	1.84	LU23	LU1234	
0286	23	F	166	115	1.57	RM12	RM12	Contracted RM found
0243	21	M	175	150	1.83	RM12	RM12	
0238	27	M	178	156	1.88	RM12	RM12	Contracted RM found
0229	24	M	180	163	1.93	RM12	RM12	Preoperative sputum, 60 cc. per day
0345	21	M	178	150	1.85	RM12	RM12	Postoperative-fluid level, cleared in 20 days
0205	34	M	166	121	1.61	RM12	RM12	
0482	25	M	173	150	1.70	LL24		Pleural thickening at left base; no surgery
0362	22	M	169	164	1.85	LL23	LL234	Contracted LL found; parenchymal air leak for 5 days postoperatively
0335	27	M	185	173	2.02	RM12	RM12	
3-Segment Group								
0116	22	M	189	160	1.98	LL24, LU4		Refused surgery
0108	25	M	170	140	1.74	LL234	LL234	Preoperative sputum, 60 cc. per day
0029	22	M	179	162	1.92	LL234	LL234	
0007	19	M	185	153	1.92	LL234	LL234	
0405	23	M	180	150	1.86	LL234	LL234	Contracted LL found
0015	18	M	180	177	1.98	LL234	LL234	‡ Preoperative sputum, 65 cc. per day; phrenic with surgery; mild empyema postoperatively
0067	19	M	183	131	1.78	LL234	LL234	Atelectasis on second, third, and fourth postoperative days
4- and 5-Segment Group								
0022	20	M	178	148	1.84	LL1234	LL1234	‡ Preoperative sputum, 75 cc. per day; phrenic with surgery; empyema postoperatively
0366	20	M	168	142	1.73	LL1234	LL1234	
0155	18	M	185	143	1.86	RL2345	RL2345	
0040	22	M	159	119	1.54	LL1234	LL1234	‡ Phrenic at time of surgery; atelectasis second postoperative day; mild empyema postoperatively
0403	17	M	185	143	1.86	LL1234	LL1234	‡ Atelectasis of LU 5 times in first 7 postoperative days

0232	22	M	179	178	2.00	LU34, LL234	LU34, LL234	Parenchymal leak for 1 week; slight pleural thickening
0224	22	M	166	152	1.77	RL12345	RL12345	
0053	57	M	171	154	1.82	LL234, LU34		
0030	20	M	180	156	1.90	RL12345	RL12345	Preoperative sputum, 50 cc. per day
0028	20	M	180	123	1.72	LL234, LU34		Refused surgery
0305	20	M	191	170	2.06	LL1234	LL234	Preoperative sputum, 55 cc. per day; small postoperative fluid level for 20 days
0020	21	M	185	150	1.90	RM12, RL235		Refused surgery
0006	18	M	183	148	1.87	LL234, LU34	LL234, LU34	‡ Phrenic at time of surgery; atelectasis on first and second postoperative days with air leak until twelfth postoperative day
0416	28	M	185	170	2.00	LL1234	LL1234	
0100	20	M	178	156	1.87	Not known	LL1234	‡ Operated elsewhere; postoperative empyema
						6- and 7-Segment Group		
0072	33	M	173	143	1.84	LU234, LL1234	LU1234 LL1234	
0330	25	M	170	140	1.74	LU34, LL1234	LU34, LL1234	‡ Preoperative sputum, 75 cc. per day; mild postoperative empyema
0017	22	M	183	190	2.08	RM12, RU3 RL2345	RM12, RL2345	Day of operation chest reopened for control of hemorrhage; uneventful postoperative course thereafter
0258	24	M	178	142	1.81	RM12, RL2345	RM12, RL2345	Parenchymal air leak for approximately 2 weeks postoperatively, with pleural thickening at base
0102	21	M	179	125	1.72	RM12, RL12345	RM12, RL12345	Postoperative empyema with 50 per cent reduction in diaphragmatic motion
0014	24	M	169	149	1.76	RM12, RL12345	RM12, RL12345	

* Key to designation of segments found by bronchography to be diseased:
Left upper lobe (LU):
(1) apical-posterior, (2) anterior, (3) lingula superior, (4) lingula inferior
Left lower lobe (LL):
(1) superior, (2) anterior-medial basal, (3) lateral basal, (4) posterior basal
Right upper lobe (RU):
(1) apical, (2) posterior, (3) anterior
Right middle lobe (RM):
(1) lateral, (2) medial
Right lower lobe (RL):
(1) superior, (2) medial basal, (3) anterior basal, (4) lateral basal, (5) posterior basal

† Postoperative course uneventful unless otherwise stated.

‡ Diaphragmatic motion on side of resection was 25 per cent less than on opposite side.

TABLE 1 B

PHYSICAL CHARACTERISTICS AND CLINICAL DATA OF 26 PATIENTS WITH BILATERAL BRONCHIECTASIS

LABORATORY NUMBER	AGE (YEARS)	SEX	HEIGHT (CM.)	WEIGHT (LBS.)	BODY SURFACE AREA (m^2)	NUMBER AND LOCATION OF SEGMENTS*				REMARKS†
						Diseased		Resected		
						Right	Left	First Operation	Second Operation	
5- to 6-Segment Group										
0326	28	M	185	158	1.90	RM12	LL234	RM12		Small amount of fluid level for 23 days postoperatively
0346	35	F	160	140	1.69	RL25	LU34	LU34		
0070	20	M	188	157	1.88	RM12	LL24	RM12	LL24	Preoperative sputum, 60 cc. per day
0256	33	M	190	160	1.90	RM2 RL25	LL4 LU2			No surgery
7- to 18-Segment Group										
0043	20	M	176	146	1.85	RM12	LU34 LL234	LU34 LL234	RM12	Preoperative sputum, 90 cc. per day; second operation—contracted RML found; atelectasis LL1 on second postoperative day
0124	23	M	183	150	1.93	RL245	LU4 LL234	LU4 LL234	RL2345	Second operation—air fluid level on eighth to fourteenth postoperative days
0128	19	M	178	130	1.77	RL235 RM12	LL24	RM12 RL2345		Preoperative sputum, 110 cc. per day; parenchymal air leak for 5 days postoperatively
0233	21	M	180	155	1.94	RL12345	LL1234	LL1234		Atelectasis of LUL second postoperative day; air space on tenth to fourteenth postoperative days
0023	18	M	173	138	1.74	RM12	LL1234 LU234	LL1234 LU234		Preoperative sputum, 120 cc. per day
0143	21	M	177	153	1.85	RM12 RL245	LL234 LU34	LL234 LU34	RM12 RL2345	First operation—atelectasis of LL1 on second and third postoperative days
0201	32	F	161	118	1.55	RM12 RL2345	LL234 LU34	LL234 LU34		Atelectasis postoperatively LUL, second and fourth postoperative days

0038	38	M	183	194	2.10	RM12 RL2345	LL234 LU34	LL234 LU34		Preoperative sputum, 55 cc. per day; small air space fourth to seventh postoperative days; sustained asthma
0360	22	M	168	138	1.72	RU2 RM12 RL12345	LL1234 LU234			Preoperative sputum, 90 cc. per day; no surgery
0027	25	M	188	142	1.88	RM12 RL2345	LL1234 LU34	RM12 RL12345	LU34 LL234	First operation—brisk parenchymal air leak for 14 days
0255	32	M	173	113	1.60	RU123 RM12 RL12345	LU1234 LL1234			No surgery
0012	24	M	183	165	2.01	RL2345	LU34	RL2345	LU34	First operation—air space with leak from first to thirteenth postoperative days
0021	31	F	162	114	1.57	RL235 RM1 RU3	LU34 LL24	LU34 LL234		Several bouts of hemoptysis in past 20 months postoperatively
0001	34	M	174	124	1.67	RL3	LU34 LL234	LU34 LL234		‡Phrenic at time of surgery; atelectasis first postoperative day; sustained asthma postoperatively
0005	23	M	168	122	1.62	RM2 RL235	LL234	RL2345	LL1234	First operation—late air space for 2 days
0454	19	F	157	118	1.52	RM12	LL1234	LL1234	RM12	First operation done elsewhere
0356	31	M	175	170	1.93	RU3 RM12 RL125	LU34 LL234	LU34 LL234	RM12 RL25	Third operation—RL1 resected followed by late air space; mild dyspnea
0455	29	M	173	174	1.93	RM12 RL2	LU234 LL1234	LU1234 LL1234		
0003	46	M	187	202	2.21	RU3 RM12 RL5	LU34 LL234	LU34 LL234	RM12	First operation—air space with parenchymal leak for 38 days postoperatively; slight pleural thickening
0202	37	M	169	121	1.79	Diffuse	Diffuse	RM12 RL5		Jaundice on thirty-first postoperative day
0408	19	M	157		1.62	RU123 RM12 RL12345	LU1234 LL1234			Operative death
0501	25	M	173	118	1.63	RL25	LL234			Recent study

* Key to designation of segments found by bronchography to be diseased: *See* table 1A.

† Postoperative course uneventful unless otherwise stated.

‡ Diaphragmatic motion on side of most recent resection was 25 per cent less than on opposite side.

whose cardiopulmonary function was quantitatively evaluated. Forty of these patients were studied in the Cardiopulmonary Function Laboratory both pre- and postoperatively, while 12 were studied only before operation and an additional 12 only after their surgery. Clinical data are listed in tables 1*A* and *B*. Most of the patients were young men in the Armed Forces. Ten were less than twenty years of age, 40 between twenty and twenty-nine, 11 between thirty and thirty-nine, and only 3 were more than forty years old. Five patients were women. The extent of disease was measured by bronchography and expressed as the number of bronchopulmonary segments involved (10). Of the 38 patients with unilateral bronchiectasis, 10 had involvement of two segments, 7 of three segments, 15 of four or five segments, and 6 had disease in six or seven segments. Twenty-six patients had bilateral bronchiectasis. Four of these had involvement of three to five segments and, in 22, seven to eighteen segments were affected.

The majority of postoperative studies were performed within two to three months after operation. Sixteen patients were studied more than six months postoperatively, but only 3 of these had been operated upon more than twelve months previously.

Methods

The tests of cardiorespiratory function employed are grouped into those which measure: (*1*) ventilation, i.e., the flow of air into and out of the lungs, including subdivisions of the lung volume; (*2*) oxygen and carbon dioxide content of arterial blood at rest and at exercise; (*3*) distribution of alveolar ventilation and perfusion; and (*4*) pulmonary artery pressures at two levels of cardiac output.

Ventilation: The maximum breathing capacity was performed by having the patient breathe through a high velocity (Collins) respiratory valve into a Douglas bag for thirty seconds. The best of three efforts was recorded in liters per minute. With the patient sitting, fractions of the vital capacity delivered in one, two, and three seconds were determined with standard equipment (11). Normal values for the timed vital capacity test are approximately 83 per cent, 94 per cent, and 97 per cent of the total vital capacity, respectively.

The subdivisions of the total lung volume were determined in the supine position. Inspiratory capacity and expiratory reserve were obtained by selecting the best of two or three closed spirometry tracings of the vital capacity. One or more recordings of the expiratory reserve were made from the respiratory midposition. Functional residual volume was measured using a modification (12) of an open-circuit oxygen-dilution method (13). Duplicate determinations were done routinely and were repeated when found to differ by more than 200 cc. Samples of alveolar air collected at the end of a seven-minute period of U.S.P. oxygen breathing were analyzed for nitrogen content (index of intrapulmonary mixing of respiratory gases). The normal value in this laboratory does not exceed 1.5 per cent nitrogen. Residual volume was calculated by subtracting the expiratory reserve from the lower figure for functional residual volume.

Resting minute ventilation and oxygen consumption were calculated from the closed spirometer tracings, and the ventilatory equivalent (minute ventilation in liters per 100 ml. of oxygen uptake) was computed therefrom. Walking ventilation in liters per minute was measured by collecting in a Douglas bag the volume of air expired through a low resistance valve during a three-minute period in which the patient walked 180 feet per minute on a level surface.

In addition to the ventilatory equivalent, a number of figures were derived using terminology described by others. Among these were the following: air velocity index (per cent of predicted maximum breathing capacity/per cent of predicted vital capacity) (14), breath-

TABLE 2

CHANGES IN VOLUME WITH VAPOR TENSION CORRECTION

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	VITAL CAPACITY SUPINE				MAXIMUM BREATHING CAPACITY				OXYGEN UPTAKE		RESTING MINUTE VENTILATION	
	BTP Saturated at Ambient T°		BTP Saturated at 37°		BTP Saturated at Ambient T°		BTP Saturated at 37°		BTP Saturated at Ambient T° cc./Min.	BTP Saturated at 37° cc./Min.	BTP Saturated at Ambient T° L/Min.	BTP Saturated at 37° L/Min.
	Liters	Per Cent Predicted	Liters	Per Cent Predicted	L/Min.	Per Cent Predicted	L/Min.	Per Cent Predicted				
0143												
Preoperative	4.027	89.9	4.179	93.3	118.1	84.4	116.5	83.2	335	348	7.175	7.462
3 months	3.235	72.2	3.350	74.8	82.0	58.6	80.6	57.6	319	331	5.416	5.620
7 months	3.728	83.3	3.865	86.3	123.4	88.1	120.5	86.1	243	252	6.221	6.466
* 2 months	2.085	46.6	2.168	48.4	86.7	61.9	85.5	61.1	202	210	4.200	4.375

* Second operation.

BTP—Body temperature and pressure.

ing reserve (maximum breathing capacity-minute ventilation at rest or exercise/maximum breathing capacity) (15), walking index ((walking ventilation/maximum breathing capacity) × 100) (16), and capacity ratio (residual volume/total lung volume) (15).

The carbon dioxide content and oxyhemoglobin saturation of arterial blood were determined with patients in the postabsorptive state at rest and immediately following acute exercise (30-step test) (15), using standard Van Slyke manometric techniques. The minute ventilation before, during, and for the first five minutes following exercise were recorded and the breathing reserve was calculated for each of these intervals.

Bronchospirometry was performed using Carlens catheters (17, 18).

A note on the constants used in expressing certain gas volumes is required in order that these data may be compared with the data from other studies. Maximum breathing capacity, walking ventilation, supine vital capacity, and respiratory volumes collected during the test of exercise tolerance indicate the volume that the collected gas would occupy at body temperature, ambient barometric pressure, and saturated with water vapor at ambient rather than body temperature. This departure from convention was noticed after the data had been tabulated and analyzed. The magnitude of the difference between this expression and BTPS[4] is indicated for one patient in table 2. Vital capacity and maximum breathing capacity volumes in this patient were collected over a representative range of ambient temperatures.

It should also be indicated that predicted values for maximum breathing capacity and residual volume are based upon equations derived from figures obtained or expressed differently from those in the present study. The predicted values for maximum breathing capacity used in this report are based upon data obtained by using a rebreathing technique (15). In 10 normal subjects in the military age group, the technique employed gave results which were 6 per cent higher than those which would be predicted. Whereas the functional residual volumes herein reported are at BTPS, predicted values are at STPD.[5] The difference in these two methods of expression is approximately 10 per cent.

Although these discrepancies are regretted, they do not affect the pre- to postoperative changes in ventilatory function.

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[4] Body temperature, ambient pressure, and saturated at body temperature.

[5] Standard temperature and pressure, dry.

Arterial blood gas content at rest and following exercise: As indicated above, these determinations were performed as a part of the test of tolerance for abrupt exercise.

Distribution: Determinations of physiologic dead space and venous admixture were performed in some patients with bilateral disease. These measurements represent, on the one hand, the volume of air ventilating surfaces, including alveoli, which are not perfused or which are poorly perfused and, on the other hand, the volume of blood which perfuses poorly ventilated or nonventilated pulmonary tissue. Physiologic dead space (V_D) is expressed both as milliliters per square meter of body surface area (V_D/m^2) and as the ratio of dead space to tidal air (V_D/V_T). Venous admixture ($\dot{Q}_{VA}$) is expressed as a proportion of the cardiac output ($\dot{Q}_{VA}/\dot{Q}_T$). Theoretical and practical considerations concerning these physiologic measurements are among the contributions of R. L. Riley and associates (19 and 20) and J. L. Lilienthal, Jr. (21). Critical to their reliable performance are accurate determinations of respiratory quotient and of gas tensions in arterial blood. Scholander micro gas analysis technique (22) was used in calculating the former; and the bubble equilibration method of Riley and associates (23), in determining the latter. Reproducibility of laboratory results during the interval in which the patients included were studied was used as the criterion of acceptability.

Pulmonary artery pressures: After introduction of a catheter into the right heart (24) and a Cournand needle into the brachial artery, either pulmonary artery, right ventricular, right atrial, or venous pressures were recorded simultaneously with brachial artery pressures and electrocardiogram using the Sanborn Electromanometer and four-channel Poly-Viso Cardiette. Mean systolic and diastolic pressures were obtained by measurements extending over at least two respiratory cycles. Mean pressures were calculated with the use of a planimeter. Cardiac output was calculated by the direct Fick method, the mixed venous blood being obtained from the pulmonary artery and the arterial blood from the brachial during the period of ninety seconds used for collecting expired gases. Approximation of steady or basal state was indicated by close checks in oxygen consumption, respiratory quotient, and cardiac output between duplicate determinations performed on each person. With the patient supine, exercise was performed against a leg ergometer during constant electrocardiographic monitoring. Determinations of minute ventilation and oxygen consumption during this type of activity indicate that a steady state is approximated after eight minutes. Consequently, cardiac output and pulmonary artery pressures were measured between the tenth and fifteenth minute of exercise.

Statistical methods: Statistical methods (25) applied to the analysis of data included calculation of the mean, standard deviation, standard error of mean, standard error of difference between two means, and "*t*." Significance was attached to differences between means when values of P were 0.05.

RESULTS

The results are presented under four headings: (*1*) Ventilation and subdivisions of the lung volume, (*2*) saturation of arterial blood at rest and following acute exercise, (*3*) ventilation-perfusion relationships in selected cases, and (*4*) data pertaining to pulmonary artery pressures in patients with bilateral resections.

Ventilation

The effect of bronchiectasis upon tests of pulmonary ventilation: Pertinent data on the effect of bronchiectasis upon tests of pulmonary ventilation are presented in tables 3*A*, 3*B*, 4*A*, and 4*B*. In table 5 is summarized the information on tests of bilateral function by comparing the mean of performance in patients with

similar amounts of disease against the mean of performance in normal persons studied in this laboratory. All tests of pulmonary function, with the exception of the total lung volume, show significant deviations from normal with respect to ventilatory function in one or more groups of patients with bronchiectasis. The index of alveolar mixing differed from the controls in all patient groups; the vital capacity in groups including patients with involvement of more than two segments; and the maximum breathing capacity and timed vital capacity in groups including patients with disease in excess of three segments. Among the derived values, the walking index, ventilatory equivalent, and the ratio functional residual air/total capacity (FRA/TC) were useful in establishing the presence of abnormality.

It is to be observed that all deviations from the normal were in the direction of showing poorer ventilatory function than was noted in the control subjects. Moreover, the more extensive the involvement, the more numerous the tests indicating abnormality. Thus, although the two-segment group proved itself abnormal with respect to one test, the four- or five-segment group did so with six tests, and the 7- to 18-segment group with nine tests.

The analysis presented in table 6 of certain data which are presented in figure 1 represents a further attempt to establish the relationship between the extent of disease and the degree of impairment in ventilatory function. Criteria of abnormality in this table, rather than being defined in terms of a clear comparison to 10 normal persons as in table 5, were established somewhat arbitrarily but with sufficient severity to preclude the inclusion of borderline normals in the abnormal ranges. Although the groups are small, it is evident that there exists a trend relating the extent of disease with the proportion of patients performing abnormally with respect to maximum breathing capacity, residual volume, vital capacity, index of alveolar mixing, and the derived ratios, walking index and residual volume/total capacity (RV/TC).

Bronchospirometry was performed in 21 patients with unilateral disease and in 10 patients with bilateral disease. Whereas only 2 of 9 patients in the two- and three-segment groups evinced abnormalities[6] of function in the affected lung, 7 of the 12 patients with unilateral involvement in excess of three segments showed such abnormalities. Impaired contribution to oxygen uptake was present in each of the 7, poor vital capacity was found in 2, and reduced minute ventilation in one patient. It seems, therefore, that the presence of considerable bronchiectasis was compatible with reasonable distribution of function, that oxygen uptake was the most sensitive criterion to use in the detection of pathology in the unoperated lung, and that the severity of disease was related to the proportion of positive findings.

With respect to the bilateral group, only 2 of 10 patients displayed abnormal *distribution* of function between the two lungs.

Changes in ventilation due to excisional surgery for bronchiectasis: The changes

[6] Right lung: oxygen consumption, minute ventilation, or vital capacity less than 44 per cent of total; left lung: oxygen consumption, minute ventilation, or vital capacity less than 36 per cent.

TABLE 3A

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR LUNG VOLUMES, MIXING INDEX, MAXIMUM BREATHING CAPACITY, AND ONE-SECOND VITAL CAPACITY IN 38 PATIENTS WITH UNILATERAL BRONCHIECTASIS*

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	TOTAL LUNG VOLUME		RESIDUAL VOLUME		VITAL CAPACITY SUPINE		FUNCTIONAL RESIDUAL VOLUME LITERS	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN	MAXIMUM BREATHING CAPACITY		VITAL CAPACITY PER CENT TOTAL IN ONE SECOND
	Liters	Per Cent Predicted	Liters	Per Cent Predicted	Liters	Per Cent Predicted			L/Min.	Per Cent Predicted	
2-Segment Group											
0384	6.5	124	1.7	107	4.8	132	2.5	2.4	118	115	74
0286	5.1	127	1.7	206	3.5	107	2.4	0.7	92	97	73
0243	6.5	117	1.5	141	4.9	111	2.0	0.9	137	99	74
2 months	4.4	80	1.4	124	3.1	69	2.1	0.9	117	85	94
0238	6.7	123	1.6	144	5.1	117	3.0	1.3	144	105	45
2 months	5.9	107	1.5	136	4.4	100	2.7	1.2	145	106	85
0229	5.5	99	1.0	89	4.5	102	1.9	4.6	159	111	70
2 months	5.8	104	1.7	152	4.7	92	2.7	2.8	121	85	
0345	5.5	98	1.3	111	4.3	95	2.4	3.2	139	99	86
2 months	4.9	86	1.4	127	3.4	76	2.3	1.0	125	89	84
0205	5.4	110	1.3	128	4.2	105	2.1	1.0	124	111	85
2 months	4.5	91	1.3	136	3.2	80	2.1	0.7	139	125	76
0482	3.9	76	1.0	102	2.8	69	2.2	1.3	123	98	87
0362 4 months	4.6	87	1.1	103	3.5	83	1.9	1.0	122	88	
0335	6.3	111	1.4	123	4.9	107	3.0	2.3	140	96	80
2 months	6.2	109	2.2	190	4.0	87	3.1	2.0	134	92	86
3-Segment Group											
0116	5.9	99	1.9	159	4.0	84	3.1	1.5	108	73	62
0108	5.0	95	1.8	170	3.2	77	2.7	2.0	98	76	69
2 months	4.1	79	1.3	127	2.8	67	2.1	1.2	106	83	87
0029	6.0	107	1.5	129	4.6	101	2.5	1.4	150	104	68
2 months	4.8	86	1.5	135	3.3	74	2.2	0.9	94	65	64
0007					5.1	108		1.5	158	108	71
2 months	6.0	102	1.7	146	4.3	90	2.6	0.8	117	80	78
0405	6.9	121	1.9	167	5.0	110	3.2	2.1	184	132	87
3 months	6.3	111	2.3	205	4.0	88	3.4	0.4	168	120	88
0015	4.6	80	0.9	79	3.7	81	1.8	5.1	157	103	84
3 months	3.2	56	0.6	53	2.6	57	1.3	1.7	94	62	85
8 months	3.1	54	0.6	55	2.5	54	1.4	0.9	130	85	90
0067	4.9	85	0.9	77	4.0	86	2.2	1.6	150	110	79
2 months	4.7	81	1.2	104	3.5	76	2.0	0.7	105	77	78

4- to 5-Segment Group

0022		5.5		97		1.5		131		4.0		89		2.5		1.3		119		85		71	
	3 months		4.5		80		1.3		113		3.2		71		2.2		0.5		65		45		58
	9 months		4.6		82		1.6		145		3.0		66		2.5		0.8		68		49		90
0366		4.5		85		1.1		107		3.4		79		2.1		0.6		112		84			
	2 months		5.0		94		1.3		119		3.7		88		2.7		0.5		121		92		80
0155		5.7		96		1.3		111		4.4		92		3.1		1.5		86		59		65	
	2 months		5.4		93		2.2		191		3.2		68		3.3		0.7		105		73		78
0040		4.5		91		1.3		129		3.2		81		2.0		2.1		90		78		63	
	3 months		3.4		67		1.0		96		2.4		60		1.7		1.2		64		55		56
0403		4.1		69		1.1		92		3.0		63		1.8		0.6		114		79		83	
	2 months		3.8		63		1.3		111		2.5		52		2.0		1.4		81		56		86
0232		5.7		101		1.2		107		4.5		99		2.2		2.8		125		83		55	
	2 months		4.6		82		1.0		90		3.6		81		2.1		1.0		110		73		
	8 months		5.0		89		0.6		52		4.4		98		2.1		1.0		83		55		61
0224		4.5		87		0.7		64		3.9		92		1.1		0.9		117		88		69	
	2 months		4.4		85		1.4		132		3.0		73		1.7		0.9		110		83		74
0053		6.5		124		2.6		161		3.9		107		3.9		5.0		64		61		40	
0030		6.6		116		1.7		150		4.9		107		3.3		2.6		132		91		73	
	3 months		4.9		86		1.6		140		3.3		86		3.0		0.8		72		50		77
0028		5.3		92		1.1		99		4.1		90		2.1		1.4		122		93		69	
0305		5.9		98		1.9		75		5.0		103		2.2		1.1		165		105		83	
	2 months		5.1		84		1.3		106		3.8		78		2.4		2.4		125		79		81
	1 week		3.9		64		1.7		143		2.2		45		2.3		0.4						
	7 months		6.7		94		1.5		120		4.3		87		2.4		1.2		134		89		87
0020		4.9		84		1.5		124		3.5		74		2.1		2.1		95		66		62	
0006	4 months		4.5		76		1.2		100		3.3		71		1.6		3.1		89		61		68
0416	24 months		4.8		85		1.2		104		3.6		80		2.2		0.4		130		90		79
0100	3 months		5.0		89		1.4		125		3.6		80		2.3		2.4		114		80		57

6- to 8-Segment Group

0072		5.2		100		1.7		165		3.5		84		2.6		0.8		87		68		64	
	3 months		3.4		65		1.0		93		2.4		58		1.6		0.6		66		52		60
0330		6.4		121		2.7		257		3.6		86		3.1		2.6		113		88		73	
	2 months		4.7		89		1.8		175		2.8		68		2.8		1.2		102		80		69
0017	2 months		6.1		107		2.0		170		4.2		91		2.2		2.0		124		80		59
0258	24 months		4.6		84		1.6		143		2.6		69		2.4		0.8		154		115		86
0102	4 months		5.4		95		2.0		176		3.4		75		3.0		4.9		70		54		69
0014	5 months		3.7		60		0.5		50		3.1		74		1.1		2.5		104		79		72

* Unless otherwise stated the values recorded were obtained before operation.

TABLE 3B

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR LUNG VOLUMES, MIXING INDEX, MAXIMUM BREATHING CAPACITY, AND ONE-SECOND VITAL CAPACITY IN 24 PATIENTS WITH BILATERAL BRONCHIECTASIS*

LABORATORY NUMBER—TIME IN POSTOPERATIVE STUDY	TOTAL LUNG VOLUME		RESIDUAL VOLUME		VITAL CAPACITY SUPINE		FUNCTIONAL RESIDUAL VOLUME LITERS	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN	MAXIMUM BREATHING CAPACITY		VITAL CAPACITY PER CENT TOTAL IN ONE SECOND
	Liters	Per Cent Predicted	Liters	Per Cent Predicted	Liters	Per Cent Predicted			L/Min.	Per Cent Predicted	
5- to 6-Segment Group											
0326	5.5	100	1.3	113	4.3	96	2.6	1.2	83	60	76
1 week	4.7	84	2.0	179	2.7	61	2.8	2.2			
2 months	5.7	102	1.9	175	3.7	84	3.1	1.2	79	57	
0346	4.2	107	1.7	186	2.5	83	2.1	0.9	83	90	78
2 months	4.0	102	1.5	160	2.5	83	2.0	0.6	82	88	83
0070	6.7	118	1.2	107	5.5	121	2.7	1.3	143	100	62
2 months	5.8	102	1.3	114	4.5	99	1.8	2.4	107	75	71
3 months	5.6	100	0.7	65	4.9	108	1.6	2.5	144	100	81
†2 months	5.8	103	1.4	120	4.4	98	2.4	1.4	121	85	82
†6 months	6.2	109	1.6	137	4.6	102	2.6	1.5	182	127	70
0256	6.6	125	2.4	227	4.2	99	2.9	3.3	75	57	74
7- to 18-Segment Group											
0043	6.0	108	1.9	172	4.1	92	3.1	3.1	138	98	70
3 months	4.4	78	1.3	118	3.1	68	2.2	0.7	106	75	83
9 months	4.9	87	1.4	124	3.5	79	2.5	0.6	114	80	76
†3 months					2.8	64			110	78	84
0124	8.4	147	2.1	186	6.3	137	4.1	5.2	114	79	79
2 months	6.5	113	2.0	178	4.5	95	3.8	2.8	90	63	85
7 months	7.5	130	2.3	200	5.2	112	4.0	0.5	126	89	87
†2 months	5.3	92	2.2	191	3.1	67	3.8	1.2	85	59	53
0128	6.4	114	2.2	195	4.2	93	3.3	2.2	121	89	34
2 months	4.0	70	1.1	99	2.8	62	2.7	2.1	75	55	79
11 months	5.3	93	1.7	155	3.6	72	2.8	1.9	117	86	
0233	6.8	101	2.0	73	4.8	106	3.2	1.7	95	65	50
2 months	4.6	80	1.1	99	3.4	75	2.3	0.9	85	58	62
0023	5.3	95	2.3	200	3.0	67	2.6	3.4	96	72	58
2 months	4.5	81	1.6	147	2.8	64	2.5	2.8	84	63	74
7 months	5.4	97	1.4	128	2.9	66	2.3	3.7	87	64	68

0143		5.1		91		1.0		94		4.0		90		2.1		1.0		118		84		58	
	3 months		3.6		65		0.4		37		3.2		72		1.8		1.9		82		58		71
	7 months		5.3		94		1.5		138		3.7		83		2.6				123		89		79
	†2 months		3.6		64		1.5		136		2.1		46		2.4		2.1		87		62		85
0201		3.9		104		1.4		183		2.5		84		2.2		3.8		92		105		54	
	6 months		3.2		86		1.6		207		1.7		56		1.7		1.8		74		87		67
	10 months		3.5		94		1.3		173		2.2		73		1.8		1.0		74		87		66
0038		7.0		126		2.9		224		4.1		96		4.1		5.2		89		63		54	
	3 months		6.7		95		3.1		127		3.7		86		2.3		1.5		91		65		58
0360		5.5		104		2.0		189		3.5		82		2.9		5.6		102		79			
0027		7.1		123		2.6		225		4.5		98		3.4		13.5		78		56		44	
	5 months		4.9		84		1.3		111		3.6		77		2.4		0.6		69		50		52
	†2 months		4.7		81		2.8		240		1.9		41		3.5		1.5		58		42		72
0255		5.3		102		2.6		256		2.7		65		3.5		4.1		70		63		81	
0012	4 months		4.7		81		1.1		96		4.1		88		2.0		1.2		101		67		47
	10 months		5.3		92		1.6		135		3.8		81		1.6		0.9		159		105		71
	†2 months		3.8		65		1.5		125		2.3		50		2.1		0.6		58		39		84
	†6 months		4.6		80		1.6		135		3.0		65		2.2		1.4		88		59		67
0021	12 months		3.6		96		1.4		191		2.6		86		2.4		1.8		73		82		59
0001	4 months		6.5		127		3.4		269		3.4		83		4.2		4.1		51		44		38
0005	†4 months		3.6		68		1.3		123		2.3		54		2.1		1.5		66		54		57
0454	11 months		3.9		100		1.7		218		2.2		71		2.2		0.8		57		60		
0356	†2 years		5.0		94		1.6		146		3.4		81		2.4		2.4		125		92		
	†4 months		4.2		79		1.5		139		2.7		64		2.2		1.0		105		77		83
0455	2 years		3.2		60		1.7		164		1.4		34		1.8		1.6		29		21		52
0003	7 months		5.4		97		1.7		132		3.7		86		2.2		3.1		107		78		57
	†1 month		5.4		96		2.1		156		3.3		81		2.7		2.0		100		74		63
	†3 months		5.9		105		2.1		160		3.8		88		2.9		2.0		102		76		61
	†9 months		6.6		117		2.3		172		4.3		101		2.9		2.7		99		73		65
	†14 months		6.3		111		2.4		183		3.9		91		3.0		2.3		126		91		64
0202		5.0		97		1.8		152		3.2		80		2.8		3.3		79		66		49	
	2 months		4.0		77		1.7		140		2.3		58		2.6		1.7		73		60		78

* Unless otherwise stated the values recorded were obtained before operation.
† Second operation.

TABLE 4A

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR RESTING OXYGEN CONSUMPTION AND VENTILATION, WALKING VENTILATION, AND BRONCHOSPIROMETRY IN 38 PATIENTS WITH UNILATERAL BRONCHIECTASIS

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	OXYGEN UPTAKE CC./MIN.	MINUTE VENTILATION		BRONCHOSPIROMETRY†		
		Resting Liters	Walking* Liters	Oxygen Uptake Per Cent	Minute Ventilation Per Cent	Vital Capacity Per Cent
2-Segment Group						
0384	257	6.0	15.2			
0286	228	4.3	12.4			
0243	321	4.7	16.3			
2 months	313	6.3	20.5			
0238	308	5.7	14.7	64	55	59
2 months	331	4.6	14.0	50	51	51
0229	363	9.3	19.4			
2 months	375	7.4	22.7			
0345	354	7.3	16.9			
2 months	245	3.7	10.1	51	54	49
0205	341	5.5	19.8			
2 months	296	6.5				
0482	525	2.5	11.7	61	63	69
0362 4 months	406	5.8	14.6	30	44	36
0335	443	6.4	11.2	53	57	52
2 months	315	7.3	20.9	53	56	45
3-Segment Group						
0116	428	9.8	12.9	58	53	55
0108	296	7.0	15.7	49	55	64
2 months	364	8.8	21.3	71	55	63
0029	247	5.8	14.9	75	64	78
2 months	339	7.2	22.6			
0007	285	7.9	17.2	55	51	53
2 months	333	7.8	20.4			
0405	293	5.6	14.6	53	52	56
3 months	238	5.4	14.2			
0015	311	7.0	16.6	64	42	50
3 months	363	8.3	17.6			
8 months	382	6.7	24.5	67	61	70
0067	305	7.9	19.6			
2 months	307	9.1	15.9	68	58	70
4- and 5-Segment Group						
0022	285	8.0	14.8	80	50	45
3 months	383	8.5	16.3			
9 months	331	8.0	17.9	63	55	69
0366	332	7.0	17.8	70	59	64
2 months	236	6.8	12.2	69	63	68

TABLE 4A—*Continued*

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	OXYGEN UPTAKE CC./MIN.	MINUTE VENTILATION		BRONCHOSPIROMETRY†		
		Resting Liters	Walking* Liters	Oxygen Uptake Per Cent	Minute Ventilation Per Cent	Vital Capacity Per Cent
4- and 5-Segment Group—Continued						
0155	416	6.1	19.4	49	47	49
2 months	323	5.3	14.1	40	46	40
0040	281	7.2	13.1	64	56	46
3 months	283	8.5	11.5	72	67	77
0403	217	6.7	19.9	63	63	54
2 months	249	4.7	24.5	76	73	74
0232	265	7.3	15.0	69	55	59
2 months	343	5.7	16.3	59		64
8 months	432	5.1	15.4	71	83	60
0224	265	5.1	10.2	52	40	49
2 months	240	4.2	12.6	51	53	53
0053	363	7.8	18.5	74	52	63
0030	335	9.6	21.7	64	64	59
3 months	289	7.8	11.5	55	51	61
0028	214	5.6	18.6	76	69	75
0305	373	8.4	17.7	82	56	60
2 months	250	5.8	14.3	71	63	68
1 week	339	6.8				
7 months	377	7.9		63	68	67
0020	267	7.8	15.5			
0006 4 months	236	7.3	16.6	60	52	63
0416 24 months	349	5.0	17.6	71	68	72
0100 3 months	208	9.1	18.7	70	55	63
6- to 8-Segment Group						
0072	397	8.3	15.6			
3 months	350	8.7	15.8			
0330	290	4.9	13.4	69	64	62
2 months			18.8	58	41	75
0017 2 months	328	8.2	16.5	32	50	30
0258 24 months	260	5.0	16.3	36	34	41
0102 4 months	267	8.7	20.1			
0014 5 months	308	10.8	16.3	29	26	38

* Ventilation while walking 180 feet per minute on level surface.

† Values for right lung reported as per cent of total.

TABLE 4B

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR RESTING OXYGEN CONSUMPTION AND VENTILATION, WALKING VENTILATION, AND BRONCHOSPIROMETRY IN 24 PATIENTS WITH BILATERAL BRONCHIECTASIS

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	OXYGEN UPTAKE CC./MIN.	MINUTE VENTILATION		BRONCHOSPIROMETRY†		
		Resting Liters	Walking* Liters	Oxygen Uptake Per Cent	Minute Ventilation Per Cent	Vital Capacity Per Cent
3- to 5-Segment Group						
0326	321	4.7	15.8	52	56	52
1 week	299	5.5				
2 months	300	6.7	16.6	54	43	
0346	282	6.2	22.7			
2 months	275	6.6	22.3			
0070	368	6.9	13.0			
2 months	342	6.1				
3 months	290	6.0	17.4	76	50	66
‡2 months	369	4.9	17.6	54	55	58
‡6 months	332	5.7	15.3	80	74	57
0256	304	8.1	21.4	51	50	58
7- to 18-Segment Group						
0043	307	6.3	25.9	52	63	72
3 months	283	6.2	25.4	67	66	76
9 months	341	6.0	17.4	79	65	72
‡3 months	335	3.7	21.0			
0124	288	8.3	21.0	61	51	48
2 months	236	4.5	17.3	32	53	61
7 months	289	5.7	9.8	65	75	64
‡2 months	206	6.7	16.9	65	65	52
0128	260	7.1	15.0	72	56	58
2 months	303	4.5	8.8	56	53	68
11 months	330	3.2	13.3			
0233	375	7.7	21.4			
2 months	304	7.3	29.5			
0023	257	6.0	13.2	52	63	54
2 months	264	8.3	12.2	81	71	72
7 months	290	5.7	15.4			
0143	335	7.2	22.6			
3 months	319	5.4	18.9			
7 months	243	6.2	11.8	62	51	66
‡2 months	202	4.2	21.4			
0201	448	7.2		58	59	63
6 months	286	6.3	18.8	64	57	61
10 months	365	4.0	17.8			
0038	502	6.1	16.0			
3 months	239	7.1	18.0	64	64	61
0360	343	8.1	25.9	49	46	49

TABLE 4B—*Continued*

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	OXYGEN UPTAKE CC./MIN.	MINUTE VENTILATION		BRONCHOSPIROMETRY†		
		Resting Liters	Walking* Liters	Oxygen Uptake Per Cent	Minute Ventilation Per Cent	Vital Capacity Per Cent
7- to 18-Segment Group—Continued						
0027	318		12.8	53	65	60
5 months	224	6.5	17.8	45	55	34
‡2 months	258	6.5	15.1	50	56	56
0255	286	6.5	25.4	56	54	56
0012 4 months	362	9.8	16.2	53	53	56
10 months	345	8.3	20.5			
‡2 months	326	5.9	20.7	50	54	56
‡6 months	363	6.4	20.5	53	61	56
0021 12 months	186	6.3	18.1	72	68	69
0001 4 months	366	6.9	14.1	74	61	65
0005 ‡4 months	290	5.7	16.9	67	52	65
0454 11 months	203	4.9				
0356 ‡2 years	341	5.2	15.8	60	54	57
‡4 months	187	5.7	19.2			
0455 2 years	467	4.3	17.8			
0003 7 months	367	6.5	17.9	75	56	65
‡1 month	297	7.9	13.6			
‡3 months	286	8.5	18.9			
‡9 months	361	6.6	19.6	66	58	64
‡14 months	349	6.5	17.9	65	60	64
0202	285	6.6	15.2			
2 months	260	9.5	25.4			

* Ventilation while walking 180 feet per minute on level surface.

† Values for right lung reported as per cent of total.

‡ Second operation.

in function attributable to operation in 32 patients with uncomplicated postoperative courses are presented in table 7, data from which are charted in figure 2. An attempt was made to differentiate those differences between pre- and postoperative results which could be assigned to removal of bronchiectatic lung from those arising as the result of variations inherent in the methods of evaluation or due to thoracotomy per se. Toward this end, the means of changes occurring spontaneously in 10 normal unoperated subjects and in 11 patients with tuberculomas for whom resections of less than one segment were performed were compared statistically to the means of changes observed in the patients with segmental resections for bronchiectasis. The method of comparison is indicated in the legend for table 7.

It may readily be seen that determinations of total lung volume, vital capacity, and maximum breathing capacity were sensitive indices for the extent of resection, whereas the other tests listed were not. "Thoracotomy" and removal of

TABLE 5

THE GROUP MEAN VALUES FOR PULMONARY FUNCTION TESTS IN NORMAL SUBJECTS AND IN 46 UNOPERATED PATIENTS WITH VARYING DEGREES OF BRONCHIECTASIS

GROUP	NUMBER OF PATIENTS	TLV PER CENT PREDICTED	RV PER CENT PREDICTED	VC PER CENT PREDICTED	MBC PER CENT PREDICTED	WALKING INDEX	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN	TVC 1' PER CENT	VENTILATORY EQUIVALENT	RV/TC PER CENT	FRA/TC PER CENT
Control Group											
Normal	10	115	125	112	106	11	0.6	82	1.6	21	37
Bronchiectasis Group											
Unilateral											
2-Segment	9	109	128	105	103	12	2.0*	75	2.2	24	42
3-Segment	7	98	130	92*	100	12	2.0*	74	2.1*	26	46*
4- or 5-Segment	12	97	111	92*	82*	17*	1.7*	66*	2.4*	25	43
6- to 8-Segment	2	110	211	85*	78	15	1.7	68	1.9	38	50
Bilateral											
4- or 5-Segment	4	112	165	92*	84*	19*	1.9*	72*	1.9	29	45*
7- to 18-Segment	12	111	188*	91*	77*	18*	5.1*	58*	2.4*	35*	52*

* Significantly different from normal group.

TLV = total lung volume
RV = residual volume
VC = vital capacity
MBC = maximum breathing capacity
TVC 1' = Timed vital capacity at one second
RV/TC = residual volume/total capacity
FRA/TC = functional residual air/total capacity

two segments were found to lower vital capacity. A significant increment in this impairment was demonstrated by the three-segment and four- or five-segment groups. The fall recorded for the six- to eight-segment group was significantly greater than that recorded for the normal and local enucleation groups but was not of different magnitude from that observed in the smaller resections.

With respect to maximum breathing capacity and total lung volume, loss of function was significantly greater following resections of three or more segments than following either no operation or a local enucleation.

TABLE 6

THE PROPORTION OF 46 UNOPERATED BRONCHIECTATIC PATIENTS, CLASSIFIED AS TO EXTENT OF DISEASE, WHO HAVE ABNORMAL VALUES IN CERTAIN PULMONARY FUNCTION TESTS*

EXTENT OF DISEASE	NUMBER OF PATIENTS	MBC <80 PER CENT OF PREDICTED	RV >156 PER CENT OF PREDICTED	VC <84 PER CENT OF PREDICTED	WALKING INDEX >15	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN >2.0	TVC 1' <62 PER CENT	VENTILATORY EQUIVALENT >2.5	RV/TC >33 PER CENT
Unilateral									
2 Segments.....	9	0	11	11	22	22	11	44	0
3 Segments.....	7	29	43	29	14	14	0	29	14
4 or 5 Segments..	12	42	8	33	55	42	9	64	17
6 to 8 Segments..	2	50	100	0	50	50	0	0	50
Bilateral									
4 or 5 Segments..	4	50	50	25	75	25	0	25	50
7 to 18 Segments.	12	67	83	33	67	92	73	27	67

* The values for MBC, RV, VC, and TVC considered as abnormal indicate a functional impairment of 25 per cent as compared with the normal control group. The upper limits of normality for ventilatory equivalent, index of alveolar mixing, walking index, and RV/TC were chosen on the basis of experiences in this and other laboratories.

See table 5 for explanation of abbreviations.

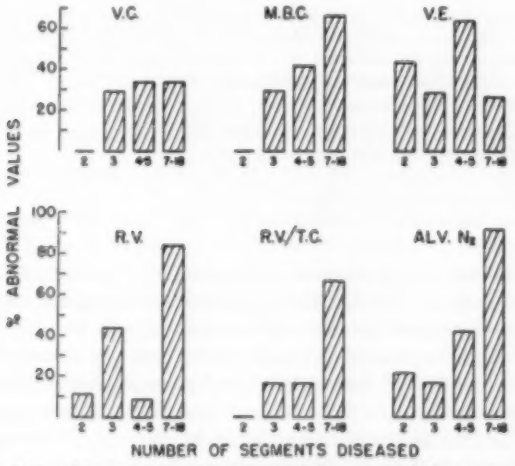

FIG. 1. The relationship between the extent of disease and the proportion of patients performing abnormally with respect to some pulmonary function tests (tables 5 and 6). V.C. = vital capacity; M.B.C. = maximum breathing capacity; V.E. = ventilatory equivalent; R.V. = residual volume; R.V./T.C. = ratio of residual volume/total lung volume; ALV. N_2 = per cent of nitrogen in alveolar air after patient has breathed oxygen for seven minutes.

Note: With the exception of ventilatory equivalent, there is, in general, a relationship between extent of disease and proportion of abnormal patients.

TABLE 7

PREOPERATIVE TO POSTOPERATIVE PULMONARY FUNCTION CHANGES IN 32 PATIENTS WITH BRONCHIECTASIS, IN 11 PATIENTS WITH TUBERCULOMAS, AND THE CHANGES OCCURRING SPONTANEOUSLY IN 10 NORMAL UNOPERATED SUBJECTS*

GROUP	NUMBER OF PREOPERATIVE TO POSTOPERATIVE COMPARISONS	TLV	RV	VC	MBC	WALKING VENTILATION	INDEX OF ALVEOLAR MIXING	TVC	VENTILATORY EQUIVALENT
Control Group									
Normal	10	−2	−0.2	−0.9	0.5	−3	0.09	−0.3	−0.2
Local enucleation, tuberculosis	11	−7	7.0	−12.0†	2.0	11	−0.5	3.0	−0.3
Bronchiectasis Group									
2-Segment	11	−8	5	−12†	−11	11	−0.6	10.0	0.0
3-Segment	6	−20‡	11	−20§	−20‡	19	−0.5	7.0	−0.8
4-or 5-Segment	12	−20‡	21	−25§	−20‡	−12	−1.8	9.0†	0.0
6-to 8-Segment	6	−25‡	−1	−27‡	−19‡	−4	−1.5	14.0	−0.3

* Figures for TLV, RV, VC, MBC, walking ventilation are group mean per cent changes as expressed by the ratio: difference between results of two studies divided by the value for the initial (preoperative) study. Figures for TVC, index of alveolar mixing, and ventilatory equivalent are group mean for difference between two studies. (−) indicates a fall; all other figures indicate a rise. Time interval between studies in the normal group was about one month. The local enucleation and bronchiectasis groups were studied one or two weeks before and less than six months after operation. All bronchiectatic patients with uncomplicated postoperative courses are included. If bilateral operations were performed, the study prior to the second operation is the "initial" study.

† Significant difference from normals.

‡ Significant difference from normals and local enucleations.

§ Significant difference from two segment group.

Absence of symbol denotes lack of statistically significant difference from either normal, local enucleation, or two-segment groups.

See table 5 for explanation of abbreviations.

Attention is invited to the increase in maximum breathing capacity recorded for the local enucleation group. This apparently misleading observation presumably may be explained by the difference in muscle tone and psychologic orientation to respiratory exertion which exists between a preoperative tuberculous patient on strict bed rest regimen and a postoperative patient enjoying some freedom of activity and from whom the significant tuberculous focus has been excised. The increase in performance under the latter circumstances might well obscure the usual effect of thoracotomy.

It is apparent that all changes of statistical significance indicate impairment. A possible exception to this general decline is indicated by the consistent fall in index of alveolar mixing, suggesting improvement in the intrapulmonary mixing of respiratory gases. Of 43 pre- to postoperative comparisons in 37 patients, there were only 4 patients who showed increased index values following surgery.

Bronchospirometry was performed in 23 patients. Of 13 patients with unilateral disease who had both pre- and postoperative tests, 3 showed improvement of

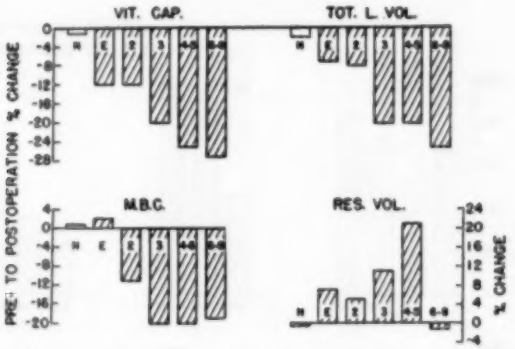

FIG. 2. Preoperative to postoperative pulmonary function changes (table 7). N = normal controls; E = patients with local enucleations for tuberculosis; figures in bars indicate number of segments excised at operation.

Note: (*1*) changes due to operation, with exception of residual volume in the 6- to 8-segment group, indicate impaired function; (*2*) relationship between extent of resection and magnitude of functional loss due to operation; (*3*) differences between enucleation and segmental resection groups.

function on the side of operation, 4 demonstrated impairment, and in 6 no noteworthy change was observed. Among 10 patients with bilateral disease studied both pre- and postoperatively, 2 were improved, 4 demonstrated impairment, and 4 showed no change.

Pulmonary function tests in patients operated upon for bronchiectasis: Tabular data on the pulmonary function of 51 patients operated upon for bronchiectasis are summarized in tables 8 and 9. Figure 3 is a graph of information selected from table 9. As in the previous discussion, the bronchiectasis groups are compared with both normal unoperated subjects as well as with patients who have had a thoracotomy with removal of minimal lung tissue. The latter can be seen to differ significantly from the normal persons in terms of vital capacity, index of alveolar mixing, timed vital capacity, and the ratio residual volume/total lung volume. Function in one or more bronchiectasis groups was significantly different from that in the enucleation group, as indicated by vital capacity, maximum breathing capacity, total lung volume, index of alveolar mixing, and the derived values, walking index and functional residual air/timed capacity. With respect to these tests, therefore, these particular bronchiectasis patients were more abnormal than those patients who had local enucleations. In addition, although a number of them compared with the enucleation group, they differed from the normal persons in regard to every test listed except residual volume.

It is evident that these laboratory determinations reveal a number of differences between bronchiectasis patients studied postoperatively and normal persons. Moreover, the departure from normality is generally related to the extent of resection. This is clearly shown by the figures for vital capacity and maximum breathing capacity, for example.

A further point of interest is found in comparing a group of patients with a

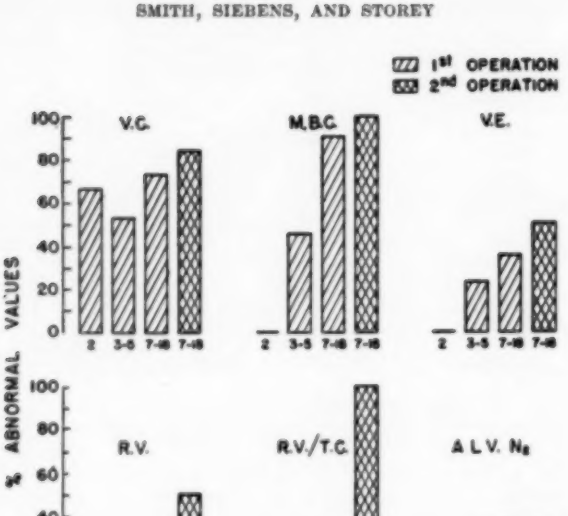

FIG. 3. The relationship between extent of resection and the proportion of patients performing abnormally with respect to some pulmonary function tests (tables 8 and 9). Abbreviations same as in figure 1.

Note: (*1*) relationship between extent of resection and proportion of patients performing abnormally; (*2*) higher incidence of abnormality in vital capacity and maximum breathing capacity than in preoperative group (figure 1).

unilateral three- to five-segment resection who pursued uncomplicated postoperative courses with a similar group who had a complicated postoperative course. Figures indicate that in many respects the latter fell near the performance level of patients with bilateral disease for whom bilateral operations had been performed.

In table 9, which is comparable to table 6, the relationship is indicated which exists between extent of resection and proportion of patients falling below a certain functional standard. This relationship is particularly striking with respect to maximum breathing capacity. Comparison of the complicated and uncomplicated three- to five-segment groups calls attention again to the functional loss incurred as a result of postoperative complications.

Bronchospirometry was performed in 32 patients. Sixteen of 25 patients with unilateral resections upon whom bronchospirometry was performed postoperatively had abnormal[6] findings on the side of operation. Unusual reduction of oxygen consumption and vital capacity was present in 14 subjects, and 9 patients showed a similar reduction in minute ventilation. Although the oxygen uptake was the most sensitive index of unilateral disease preoperatively, in this

TABLE 8

THE GROUP MEAN VALUES FOR PULMONARY FUNCTION TESTS IN NORMAL SUBJECTS AND IN PATIENTS STUDIED LESS THAN SIX MONTHS FOLLOWING LOCAL ENUCLEATIONS FOR TUBERCULOSIS OR RESECTION FOR BRONCHIECTASIS

GROUP	NUMBER OF PATIENTS	TLV PER CENT PREDICTED	RV PER CENT PREDICTED	VC PER CENT PREDICTED	MBC PER CENT PREDICTED	WALKING INDEX	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN	TVC 1′ PER CENT	VENTILATORY EQUIVALENT	RV/TC PER CENT	FRA/TC PER CENT
Control Group											
Normal	10	115	125	112	106	11	0.6	82	1.6	21	37
Local enucleation	11	109	148	97§	99	13.3	1.2§	71§	2.0	28§	45
Bronchiectasis Group											
*Unilateral**											
2-Segment	6	100	132	90§	99	12	2.0‖	81§	2.2	26	44§
3-to 5-Segment	13	89‖	134	80‖	80‖	15	1.0	79	2.3§	30	48§
6-to-8-Segment	5	89§	154	73‖	70‖	20§	2.6‖	66‖	2.9§	32§	50
Bilateral†											
4-to-5-Segment, first operation	4	94§	148	81§	70‖	23§	1.6§	77	2.6§	34§	54
7-to-18-Segment, first operation	11	85‖	131	74‖	65‖	21‖	1.8‖	71§	2.3§	32§	54‖
7-to-18-Segment, second operation	6	82‖	157	60‖	59‖	21‖	1.6§	66§	2.5§	39§	63‖
Complicated‡											
3-to-5-Segment (unilateral)	6	73‖	78‖	65‖	60‖	20‖	1.3§	70§	2.8§	26	45§

* With the exception of one case in which residual disease remained after operation, the extent of surgery corresponds to the extent of involvement.

† Inasmuch as patients with bilateral disease have a unilateral resection at each operation, contralateral disease is present at the time of the study following the first operation.

‡ Diaphragmatic motion on the operative hemithorax was less than 25 per cent as compared with the contralateral side.

§ Significantly different from normal group.

‖ Significantly different from normal and local enucleation groups.

See table 5 for explanation of abbreviations.

group of postoperative patients impaired vital capacity appeared equally frequently. Seven patients had bronchospirometric studies following bilateral resections, and distribution of function between the two lungs was abnormal in 4 patients.

Saturation of Arterial Blood at Rest and Following Acute Exercise

The data pertaining to the 30-step test of exercise tolerance are recorded in tables 10*A* and 10*B*, summaries of which are presented in tables 11 and 12. Of 38 patients with bronchiectasis studied preoperatively, 8 had low (below 92.1 per cent) arterial saturations at rest, and 4 showed low saturation after exercise. Three of the former and 2 of the latter were in the bilateral group. Among the 7 patients with low arterial saturations at rest who performed the exercise test,

TABLE 9

THE PROPORTION OF BRONCHIECTATIC PATIENTS, CLASSIFIED AS TO EXTENT OF RESECTION, WHO HAVE ABNORMAL VALUES IN CERTAIN PULMONARY FUNCTION TESTS WHEN STUDIED LESS THAN SIX MONTHS FOLLOWING SURGERY*

EXTENT OF DISEASE	NUMBER OF PATIENTS	MBC <80 PER CENT OF PREDICTED	RV >156 PER CENT OF PREDICTED	VC <84 PER CENT OF PREDICTED	WALKING INDEX >15	INDEX OF ALVEOLAR MIXING PER CENT NITROGEN >2.0	TVC 1′ <62 PER CENT	VENTILATORY EQUIVALENT >2.5	RV/TC >33 PER CENT
Uncomplicated†									
Unilateral									
2 Segments	6	0	17	67	33	17	0	0	0
3 to 5 Segments	13	46	15	53	31	7	0	23	15
6 to 8 Segments	5	60	75	80	80	80	40	60	50
Bilateral									
4 to 5 Segments	4	75	50	25	0	25	0	25	75
7 to 18 Segments, 1 operation	11	91	27	73	64	36	18	36	27
7 to 18 Segments, 2 operations	6	100	50	84	100	33	50	50	100
Complicated									
Unilateral									
3 to 5 Segments‡	6	84	0	100	100	0	33	50	0
Bilateral									
7 to 18 Segments, 1 operation§	2	100	50	50	100	50	100	50	100

* The values for MBC, RV, VC, and TVC considered as abnormal indicate a functional impairment of 25 per cent as compared with the normal control group. The upper limits of normality for ventilatory equivalent, index of alveolar mixing, walking index, and RV/TC were chosen on the basis of experiences in this and other laboratories.

† Diaphragmatic motion on operative side greater than 25 per cent of the opposite side.

‡ Diaphragmatic motion on the operative side less than 25 per cent of the opposite side.

§ Complication consisted of asthma postoperatively.

See table 5 for explanation of abbreviations.

saturation was elevated by exercise in 5 and unaffected in 2. The 4 patients with low arterial saturations following acute exercise all had arterial saturations below 93.5 per cent at rest and, in 2, the saturation values were below 92 per cent. The incidence of low saturation in this series, therefore, is small, the response to a sudden bout of moderately severe exercise is varied, and correlating segmental involvement and the incidence of "unsaturation" is difficult.

In the attempt to classify patients with respect to ventilation at rest and following exercise, the semi-arbitrary limits indicated in table 11 were established. Thirty-three patients were grouped for this analysis. Four of 23 with unilateral disease and 4 of 10 with bilateral disease had unusually high resting minute ventilations. Nine of the 23 and 6 of the 10 foregoing patients failed to approximate resting ventilatory volumes five minutes after exercise. It may be concluded, therefore, that a certain proportion of patients with bronchiectasis have unusually high values for minute ventilation at rest, that in a larger number the

hyperventilation caused by exercise is prolonged unusually, and that the latter abnormality may be related to the extent of disease.

Figures for the ratio breathing reserve/maximum breathing capacity are difficult to interpret inasmuch as they reflect minute ventilation as well as maximum breathing capacity. If one uses 76 per cent as a reasonable criterion of adequate performance, however, it is again possible to show that, in exercising, a certain number of patients with bronchiectasis (5 of 23 with unilateral disease and 5 of 10 with bilateral disease) encroach on an unusually large proportion of their maximum breathing capacity.

In table 12 similar data are summarized pertaining to patients studied postoperatively. Only those who had completed their surgical treatment will be considered. Although 8 of 38 bronchiectatic patients had resting saturations below 92.1 preoperatively, none of the 36 patients studied postoperatively fell below this level. However, although 4 of the 38 preoperative patients were below 92.1 in the post-exercise period, 5 of the 36 fell below this level following the completion of surgery. One might therefore infer with reservations that, although the incidence of patients with low resting saturations is reduced by surgery, the proportion of patients with low saturations following acute exercise is less favorably affected.

With reference to ventilation, 4 of 34 patients had resting values of more than 5 liters per minute per square meter, and 11 of 33 patients ventilated in excess of 6 liters per minute per square meter five minutes after exercise. Comparable figures listed above for the preoperative group are within the same range. However, although 3 of 7 preoperative patients in the 7- to 18-segment group had elevated minute ventilations at rest and 4 of 7 had elevated values for the fifth minute following exercise, corresponding values postoperatively are one of 6 and one of 5. Although this is a small group of patients, these data suggest that minute ventilation at rest and in recovering from exercise may be reduced toward normal by operation in patients in whom these values are elevated preoperatively. Five of 23 preoperative patients with unilateral disease and 5 of 10 with bilateral disease had breathing reserves less than 76 per cent of their maximum breathing capacity before operation, while, following operation, 9 of 28 patients with unilateral and 4 of six with bilateral resections could be similarly classified. A striking observation pertaining to ventilation recorded in table 12 is the fact that 9 of 10 patients with bilateral disease fell into the poor performance category after their first operation.

Ventilation-Perfusion Relationships

Data pertaining to 8 patients with bilateral resections are included in table 13. Resting physiologic dead spaces expressed in milliliters per square meter of body surface area (V^c_D/m^2) were normal (less than 100) in all but one case and, when expressed as the ratio of dead space to tidal air (V^c_D/V_T), were abnormal (more than 30 per cent) in 3 patients. In response to exercise, the former value increased in 4 of 5 patients, and the latter expression either fell or remained in

TABLE 10 A

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR ARTERIAL BLOOD GAS ANALYSIS AND FOR VENTILATION BEFORE, DURING, AND AFTER EXERCISE IN 35 PATIENTS WITH UNILATERAL BRONCHIECTASIS

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	ARTERIAL BLOOD			VENTILATION† L./MIN./M²				
	Oxygen Saturation Per Cent		Carbon Dioxide Content Volume Per Cent	Rest	Exercise	Recovery		
	Rest	Recovery*	Rest			1 Minute	2 Minutes	5 Minutes
2 Segments								
0384	94.6	93.0	43.0	4.6	9.5	11.6	13.4	4.6
0243 2 months	94.3	93.7	47.6	4.3	15.7	11.9	8.3	5.2
0238	96.3	93.9	49.7	3.1	6.9	8.4	7.1	3.7
2 months	96.7	94.3	46.9	3.6	7.1	8.9	6.1	3.7
0229	97.4	94.3	49.1	3.9	13.8	19.2	12.4	4.2
2 months	93.1	94.3	51.6	4.4	17.6	19.8	9.0	5.2
0345	92.0		48.7	8.9	11.5	11.5	8.8	5.7
2 months	92.3	89.7	53.4	3.0	7.6	9.6	6.8	3.9
0205	95.9	93.8	44.4	6.7	12.1	14.9	9.7	7.0
2 months	94.6	95.1	44.4	4.0	12.1	11.2	10.3	5.3
0362 4 months	97.1	95.1	48.4	3.6	5.5	11.5	7.4	6.0
0335	94.0	95.5	46.2	4.0	9.8	15.0	11.9	6.4
2 months	96.8	95.8	50.5	4.7	8.6	14.2	12.1	5.4
3 Segments								
0116	95.5	93.4	45.5	3.6	12.6	9.4	7.3	4.3
0108	95.6	94.5	48.6	2.5	10.4	11.2	9.3	6.0
2 months	95.1	96.6	46.0	4.7	10.7	11.2	9.5	6.3
0405	95.7	94.0	47.4	4.2	8.9	10.9	8.2	5.4
3 months	96.7	97.9	54.8	4.6	11.6	14.0	10.0	7.3
0015 3 months	94.1	94.5	48.2	4.6	6.5	17.6	9.5	9.7
8 months	94.2	91.7	47.9	4.7	12.3	12.9	8.3	6.1
0067 2 months				4.3	11.7	9.2	8.2	4.7

4 or 5 Segments													
0022		88.2		88.1		43.3		5.3		10.1		13.1		11.6		10.4	
	3 months		95.0		93.5				4.9		9.7		10.4		10.0		5.2
	9 months		96.8		92.0		49.0		4.5		12.0		14.0		9.3		6.1
0366		96.6		95.1		47.7		5.0		8.8		14.0		9.4		6.2	
	2 months		97.6		99.1		45.6		4.9		8.0		9.5		8.8		5.8
0155		89.2		92.9		51.5		4.5		12.4		15.9		9.6		6.1	
	2 months		95.2		96.5				4.2		6.7		11.7		8.8		
0040		92.2		92.7				4.1		11.1		14.8		10.8		9.5	
	3 months		95.9		99.2		47.2		4.9		14.5		12.5		8.6		5.2
0403		91.9		97.1		47.3		4.4		9.7		12.7		8.7		5.8	
	2 months		95.4		95.7		47.9		6.4		10.9		13.5		10.2		5.5
0232		97.0		95.2		51.9		3.5		10.2		9.7		7.0		4.4	
	2 months		97.8		98.0		47.5		4.2		12.5		13.0		8.1		6.1
0224		94.2		95.3		44.4		3.4		10.2		10.4		8.4		4.3	
0053		95.5		92.2		44.9		4.6		14.2		16.1		11.2			
0030		96.1		95.4		46.2		4.2		15.5		10.5		8.1		6.0	
	3 months		94.4		98.9		47.1		4.5		10.4		11.4		8.5		5.3
0028		96.5		93.1		48.0		3.7		11.8		19.5		6.9		5.6	
0305		96.7		95.1		45.1		3.5		6.5		10.6					
	1 week		97.5		94.7		49.7		4.4		9.3		16.8		10.5		5.3
	2 months		95.6		99.0		48.8		3.9		8.1		11.7		8.0		5.0
	7 months		96.1		96.0		50.4		4.5		9.8		13.5		8.1		
0020		92.8		92.1		43.2		4.8		11.0		12.1		9.1		6.3	
0006	4 months		93.2				42.7		3.6		11.1		13.1		9.0		5.7
0416	24 months		95.9		94.9		49.5		4.2		10.2		11.4		8.0		4.6
0100	3 months		98.6		97.8		48.4		4.4		16.9		10.2		6.2		5.1
6 or 7 Segments																	
0072		96.8		94.8				4.8		12.7		13.8		10.2		7.2	
	3 months		92.9		90.7		42.1		4.3		7.9		10.8		7.4		2.8
0330		91.1		92.6		45.9		5.6		9.4		10.5		8.6		6.8	
	2 months		95.2		94.6		43.8		5.8		13.5		13.9		9.7		6.7
0017	2 months		93.1		93.0		44.1		2.2		6.5		8.4		9.3		6.9
0258	24 months		94.1		96.7		43.8		4.4		9.0		10.9		9.1		5.8
0102	4 months		92.4		96.5		46.3		5.6		14.4		12.8		8.4		6.2
0014	5 months		98.3		92.1		42.1		3.0		8.8		10.7		9.0		6.2

* The blood sample is drawn as soon as technically possible during the first minute of recovery.
† Values reported are before, during, and after one minute, 30-step exercise.

TABLE 10 B

THE PREOPERATIVE AND POSTOPERATIVE VALUES FOR ARTERIAL BLOOD GAS ANALYSIS AND FOR VENTILATION BEFORE, DURING, AND AFTER EXERCISE IN 23 PATIENTS WITH BILATERAL BRONCHIECTASIS

LABORATORY NUMBER—TIME OF POSTOPERATIVE STUDY	ARTERIAL BLOOD			VENTILATION† L/MIN/M²				
	Oxygen Saturation Per Cent		Carbon Dioxide Content Volume Per Cent	Rest	Exercise	Recovery		
	Rest	Recovery*	Rest			1 Minute	2 Minutes	5 Minutes
3 to 5 Segments								
0326	93.8	94.2	48.2	4.1	9.4	12.7	10.0	6.7
7 days	88.1	93.1	49.7	4.4	9.3	12.0	9.1	6.6
2 months	94.8	93.3	44.6	4.3	9.5	9.5	9.4	5.5
0346				4.6	10.3	12.7	10.3	5.9
0070	93.5	97.5						
2 months	94.1	90.7	44.0	3.8	5.5	11.8	7.0	3.5
‡2 months	94.2	90.8	48.6	4.3	7.7	11.6	7.2	5.1
‡6 months	97.7	98.3	47.7	3.5				
0256	92.5	93.1	43.6	5.1	11.3	12.6	11.3	6.8
7 to 18 Segments								
0043	97.0	97.5						
3 months	95.5	93.0	47.4	4.4	15.5	17.5	10.0	5.4
9 months	94.9	94.9	47.8	4.3	13.1	14.4	6.8	5.5
0124	95.2	95.4	46.2	3.8	8.4	11.9	9.5	7.1
2 months	93.1	91.8	44.9	4.4	9.5	12.3	8.9	6.2
7 months	98.0	94.5	49.0	4.3	11.9	13.3	7.7	6.2
‡2 months	95.2	92.4	51.2	4.5	9.4	11.7	8.5	6.0
0128	92.1	95.5	45.4	5.1	9.7	9.7	8.6	7.1
2 months	94.1	94.7	48.8	4.8	9.7	12.3	7.5	4.2
11 months	96.0		48.9					
0233	93.4							

0023	90.5		95.1		46.1		4.9		13.5		21.4		16.3		4.7	
2 months		91.6		92.7		50.1		4.9		11.5		10.5		7.4		5.6
7 months		93.2		91.8		48.2		5.3		11.1		5.9		6.4		6.0
0143	96.4		97.3				3.7		8.9		11.3		8.4		5.4	
3 months		96.1		94.0		46.5		4.0		10.3		13.9		8.3		4.5
7 months		98.2		92.7		48.5		4.3		11.2		10.4		7.1		5.5
‡2 months		96.7		95.2		48.5		8.2								
0201	96.1		92.5				4.7		8.8		11.4		8.2		5.2	
6 months		93.4		95.4		50.1		4.3		10.5		12.5		9.6		5.2
10 months		93.7		93.2		44.1		5.0								
0038	94.4		93.3		49.0											
3 months		97.4		93.2		44.2		3.6		10.4		14.6		9.5		5.1
0360	88.0		82.7				6.0		8.1		12.6		9.8		8.3	
Repeat test	93.5		87.5		46.3		5.1		11.9		13.7		9.4		6.5	
0027	92.0		84.7		51.9		4.3									
5 months		96.2		94.0		44.6		3.9		11.9		10.0		8.2		5.9
‡2 months		95.8		91.8		50.3		3.7		8.2		9.2		7.2		6.1
0255	93.3		88.7		50.7		7.6		16.3		17.0		14.7		10.0	
0012 ‡2 months		96.2		92.9		43.2		3.8		9.6		12.1		8.3		4.9
‡6 months		95.9		96.2		47.9		3.9		11.0		13.4		10.0		4.0
0021 12 months		99.6		93.3				6.4		12.1		12.7		9.6		5.7
0005 ‡4 months		95.4				47.2		4.0		9.3		9.7		6.7		4.6
0454 11 months		95.6		95.2		45.6		5.4		12.1		16.1		13.4		6.2
‡2 months		94.4		94.6		48.7										
0356 ‡2 years		96.3		99.1												
‡3 months		93.4		94.0		48.4										
0003 ‡14 months		95.4		93.7		49.2		3.5		10.1		11.9		8.6		4.6
0408	76.1				57.5											
0202 2 months		94.5		90.9		45.7		5.2		12.1		12.4		10.9		7.0

* The blood sample is drawn as soon as technically possible during the first minute of recovery.
† Values reported are before, during, and after one minute, 30-step exercise.
‡ Second operation.

TABLE 11

THE PROPORTION OF UNOPERATED BRONCHIECTATIC PATIENTS, CLASSIFIED BY EXTENT OF DISEASE, WHO HAVE ABNORMAL VALUES IN ARTERIAL SATURATION AND VENTILATION EITHER AT REST OR FOLLOWING EXERCISE*

GROUP	BLOOD OXYGEN SATURATION			VENTILATION				
							Breathing Reserve/ Maximum Breathing Capacity	
	Number of Patients	Rest <92.1 Per Cent	Recovery <92.1 Per Cent	Number of Patients	Rest >5L/m²	Fifth Minute >6L./m²	First Minute <76 Per Cent	Second Minute <76 Per Cent
Unilateral								
2-Segment	6	16.7	0.0	6	33.3	33.3	0.0	0.0
3-Segment	3	0.0	0.0	3	0.0	0.0	0.0	0.0
4- or 5-Segment	12	25.0	8.5	12	8.5	41.6	33.3	8.3
6- or 7-Segment	2	50.0	0.0	2	50.0	100.0	50.0	0.0
Bilateral								
3- to 5-Segment	3	0.0	0.0	3	33.3	66.7	100.0	33.3
7- to 18-Segment	12	25.0	25.0	7	42.9	57.1	28.6	28.6

* 30-step test.

TABLE 12

THE PROPORTION OF PATIENTS, CLASSIFIED BY EXTENT OF RESECTION, WHO HAVE ABNORMAL VALUES IN ARTERIAL SATURATION AND MINUTE VENTILATION EITHER AT REST OR FOLLOWING EXERCISE*

GROUP	BLOOD OXYGEN SATURATION			VENTILATION				
							Breathing Reserve/ Maximum Breathing Capacity	
	Number of Patients	Rest <92.1 Per Cent	Recovery <92.1 Per Cent	Number of Patients	Rest >5L/m²	Fifth Minute >6L./m²	First Minute <76 Per Cent	Second Minute <76 Per Cent
Unilateral								
2-Segment	7	0	14.3	7	0	0	14.3	0
3-Segment	4	0	25.0	4	0	100.0	25.0	0
4- or 5-Segment	11	0	9.8	11	9.8	18.2	45.4	18.2
6- or 7-Segment	6	0	16.7	6	33.3	66.7	33.3	0
Bilateral								
3- to 5-Segment, first operation	2	0	50.0	2	0	0	0	0
7- to 18-Segment, first operation	11	9.1	27.3	10	40.0	30.0	90.0	20.0
7- to 18-Segment, second operation	8	0	14.3†	6	16.7	20.0‡	66.7	16.7

* 30-step test.

† Based on 7 patients.

‡ Based on 5 patients.

TABLE 13

VENTILATION, DISTRIBUTION, AND PULMONARY CIRCULATION DATA IN EIGHT PATIENTS WITH BILATERAL RESECTIONS FOR BRONCHIECTASIS AND IN TWO PATIENTS WITH BILATERAL BRONCHIECTASIS WHO WERE STUDIED BEFORE OPERATION

PATIENT	AGE	MONTHS AFTER OPERATION WHEN STUDIED	EXTENT OF RESECTION*	VENTILATION							DISTRIBUTION						CIRCULATION					
				Vital Capacity		Maximum Breathing Capacity		Residual Volume		RV/TC × 100	V_D				$\dot{Q}_{VA}/\dot{Q}_T$		Cardiac Index		Pulmonary Artery Pressure			
				L	Per Cent Predicted	L/Min.	Per Cent Predicted	L	Per Cent Predicted		V^c_D/m^2	V^c_D/V_T	V^c_D/m^2	V^c_D/V_T	Rest	Exercise			Mean		Systolic/Diastolic	
											Rest		Exercise				Rest	Exercise	Rest	Exercise	Rest	Exercise
0003	46	14	LU34 LL234 RM12	3.9	91	126	91	2.4	183	38	70	21	136	27	9.8	6.0	3.1	5.5	27	32	37/15	46/22
0070	20	6	LL24 RM12	4.6	102	182	127	1.6	137	25	27	11	34	8	3.6	2.8	4.1	5.5	20	24	29/14	31/17
0124	23	2	LU4 LL234 RL2345	3.1	67	85	59	2.2	191	42	98	39	74	23	4.8	4.2	2.9	3.5	11	17	26/4	24/13
0043	20	3	LU34 LL234 RM12	2.8	63	110	79	1.5	135	35	135	40			5.8	8.2	3.4	6.1	10	16	16/7	19/10
0356	31	4	LU34 LL234 RM12 RL25	2.7	64	105	77	1.5	139	30	81	37	116	28	14.6†	7.0	2.8	5.2‡	19	30	27/16	45/21
0454	19	1½	LL1234 RM12								56	23	76	28	6.4	5.6	3.5	4.0	21	23	30/11	33/16
0012	24	6	LU34 RL2345	3.0	65	88	59	1.6	135	35	72	23			9.6							
0143	21	2	LU34 LL234 RM12 RL2345	2.1	47	87	62	1.5	136	42	71	26			3.7		4.1		21		32/11	
0501	25	Preoperative	RL25 LL234	3.1	72	158	131	0.8	77	21	81	19	71	13	10.6	6.8	4.0	5.2	19	19	25/12	24/15
0360	22	Preoperative	RU2 RM12 RL12345 LL1234 LU234	3.5	82	102	79	2.0	189	37	67	28	115	37	14.0	3.8	3.2	4.9	24	26	35/16	38/21

* See table 1 for definition of symbols.
† Unreliable because of poor R value.
‡ Based on laboratory average for A-V difference in this type of exercise.
V_D = physiologic dead space
$\dot{Q}_{VA}/\dot{Q}_T$ = proportion of cardiac output delivered to nonventilated or poorly ventilated parenchyma
RV/TC = residual volume/timed capacity
V^c_D/m^2 = physiologic dead space per square meter of body surface area
V^c_D/V_T = ratio of dead space to tidal air

the normal range in each of the 5. With respect to this determination, therefore, this group of patients with bilateral resections does not demonstrate a striking abnormality.

In the 7 patients with reliable determinations for the proportion of cardiac output delivered to nonventilated or poorly ventilated parenchyma ($\dot{Q}_{VA}/\dot{Q}_T$), 3 showed abnormally high (in excess of 6 per cent) values. Each of the 2 unoperated patients with bilateral disease who were studied had values in excess of those encountered in those who underwent surgery. In all patients studied postoperatively save one, exercise reduced the ratio $\dot{Q}_{VA}/\dot{Q}_T$. In comparing the resting venous admixtures in the postoperative cases with those for the 2 unoperated cases, therefore, one finds the suggestion that removal of bronchiectatic tissue *reduces* the proportion of cardiac output perfusing poorly ventilated alveoli.

Pulmonary Artery Pressures

Seven patients with bilateral resections and 2 preoperative patients with bilateral disease were catheterized in order to establish the effect of disease and its surgical management upon pulmonary hemodynamics. These data are recorded in table 13 and figure 4. In relating these figures to normal values, a comparison was made with the studies of both Hickam and Cargill (26) and of Riley and associates (27). The highest value for mean exercise pulmonary artery pressure (PAP) recorded by the former investigators (15 mm. of mercury) and

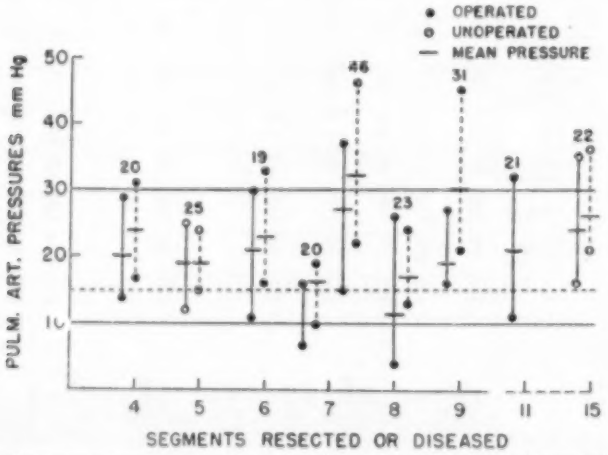

FIG. 4. Pulmonary artery pressures at rest and exercise. Solid vertical lines indicate range of resting pressures; dotted lines indicate range during exercise. Numbers are patients' ages in years. Normal limits for diastolic (10 mm. of mercury) and systolic (30 mm. of mercury) pressures are shown. Dotted horizontal line is highest mean pressure (15 mm.) recorded by Hickam and Cargill (26) in normal subjects performing exercise.

Note: Some systolic and most diastolic as well as mean pressures are moderately above normal range. Highest pressures are found in the 2 oldest patients.

the standards for systolic (30 mm. of mercury) and diastolic (10 mm. of mercury) levels adopted by the latter group were used.

Five of the 7 patients who were operated upon and both of those who had no surgery had a resting mean pulmonary artery pressure in excess of 15 mm. of mercury, and all had pressures in excess of this value during "steady state" exercise. Three of the 7 resected and one of the unoperated patients had mean resting systolic pressures of 30 or more mm. of mercury; 5 of the former group and both of the latter patients had diastolic pressures of more than 10 mm. of mercury. Corresponding figures for exercise are: 4 of 6 postoperative and one of the 2 unoperated patients had mean systolic pressures of more than 30 mm. of mercury, and all patients had mean diastolic pressures of 10 or above.

Assuming that standards adopted by other laboratories may be applied with validity, it is apparent that, in this group of patients, pulmonary artery pressures were moderately elevated.

DISCUSSION

The understanding of a given pathologic entity is limited by the precision of methods used for evaluating the disease as well as the results of its treatment. In the case of disorders of the cardiorespiratory system, analytical methods popularized within recent years (13, 15) have created both an opportunity for comprehensive evaluation of a lesion as well as a responsibility for perception with respect to its treatment. Although most of the methods used in this report are dependent upon patient cooperation and are consequently prone to subjective error, when applied to a fairly large group for which controls have been established, they form a reasonable basis for the detection of trends. Furthermore, even though they in no way supplant traditional methods for obtaining clinical impressions, their use as semi-quantitative adjuncts frequently more clearly defines where clinical distinction may be obscure, establishes the presence of abnormalities not detectable by conventional means, and generally specifies pathophysiologic processes.

Although the classification of a disease so protean in its symptomatology as bronchiectasis is difficult to categorize, the grouping of patients by extent of involvement is a useful expedient. Patients with bronchiectasis in two or three bronchopulmonary segments of one lung may be expected to show few significant differences from the unilateral or bilateral ventilatory function of normal persons in the same age group. When there is involvement of more than three segments or when bilateral disease is present, however, the differences between normal persons and bronchiectatic patients become evident. Departure from normality becomes particularly striking in patients with extensive bilateral disease. These patients generally have overdistention associated with obstruction. Although their total lung volume is normal, their vital capacity is low and their residual volume high. Timed vital capacity and maximum breathing capacity are impaired. The index of alveolar mixing is elevated. Minute ventilation at rest and exercise is commonly increased. Inasmuch as the patients reported herein were ambulatory and admitted directly from active military duty at the time of

study, these differences cannot be attributed to prolonged hospitalization for a chronic respiratory disease.

The effects of operation upon ventilation are adverse, persisting as such through the third to sixth month of recovery. Generally speaking, just as the extent of disease is related to the functional deficit, so the extent of resection is related to the functional loss. Vital capacity and maximum breathing capacity have been found to be sensitive indices for detecting differences between groups equated with respect to magnitude of resection. These tests indicate that a resection of three segments[7] or more may be expected to reduce function significantly more than removal of two segments[8] or less. Inasmuch as residual volume tends to remain constant as vital capacity falls, the drop in total lung volume mirrors the reduction of vital capacity.

A number of factors affect the magnitude of these changes: age, time, the presence of preoperative "overdistention," and the effect of complications.

With respect to *age*, Mannix and associates (28) have recently reported a study of nine patients who underwent bilateral resections for bronchiectasis. They found that their two youngest patients had the best results; and their three oldest,the poorest. The remarkable adaptation to pneumonectomy demonstrated by some young patients (29, 30) is in marked contrast to the functional loss generally incurred by patients in the older age group (31). Although the experience reported in the present study is numerically inadequate for statistical reliability, it nevertheless suggests that, other factors remaining constant, advancing age predisposes to greater functional loss. By the same token, changes attending operation in the military age group may not be considered representative of those to be expected in older patients. Finally, as will be brought out below, the highest pulmonary artery pressures recorded in 7 patients with bilateral bronchiectasis were found in the 2 oldest patients (figure 4).

Obviously this study is not adequate for judging the ultimate effects of resectional therapy. The literature (32, 33) as well as the findings in a number of the bilateral cases in the present study (2 of which are presented in figures 5*A* and *B* and 6*A*, *B*, *C*, and *D*) attest to the critical role that *time* plays in restoring ventilatory function. A statistical analysis (34) comparing vital capacity and maximum breathing capacity in 10 patients studied for two and six months following small (one or two segments) resections for tuberculosis shows that performance on these tests increased significantly ($P = 0.01$) during this four-month period. Although the increased amount of up-time allowed in the postoperative period to patients who have been practically immobilized preoperatively contributes to this change, such figures emphasize the demands healing makes upon time. For patients who are to undergo staged operations, this factor assumes paramount significance.

Concerning "overdistention," only 3 of 19 patients with resections of two, three, four, or five segments had unusually elevated[9] residual volumes postoperatively. Moreover, no significance could be attached to the changes in residual

[7] Most patients in the three-segment group had resections of basal segments.

[8] Most patients in the two-segment group had lingulectomies or right middle lobectomies.

[9] Predicted value more than 25 per cent higher than normal controls.

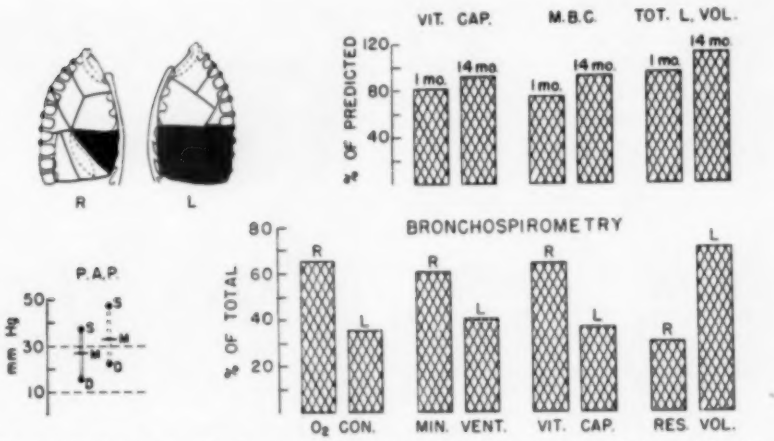

FIG. 5A. Patient Lab. #0003. Age 46. Resection of basalar segments left lower lobe, lingula, and right middle lobe. For roentgenograms, see figure 5B.

Note: moderate pulmonary hypertension, functional deficit of left lung including high residual volume, effect of time on recovery of function.

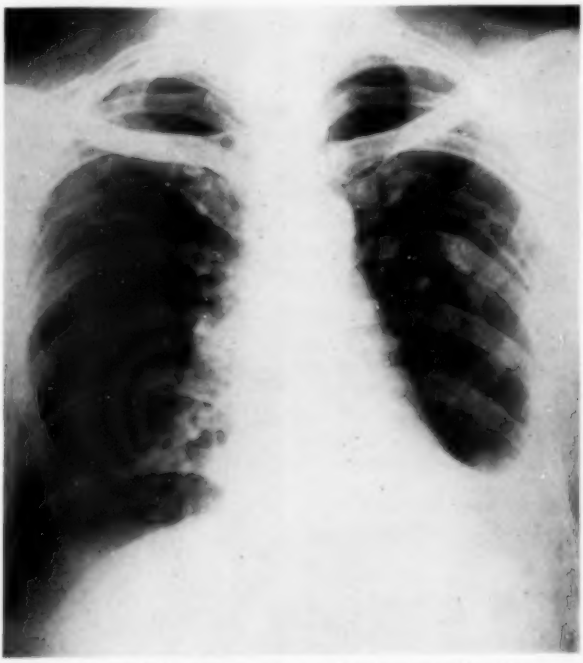

FIG. 5B. Patient Lab. #0003. Roentgenogram fourteen months after second operation. Note pleural thickening of left base and elevation of left hemidiaphragm.

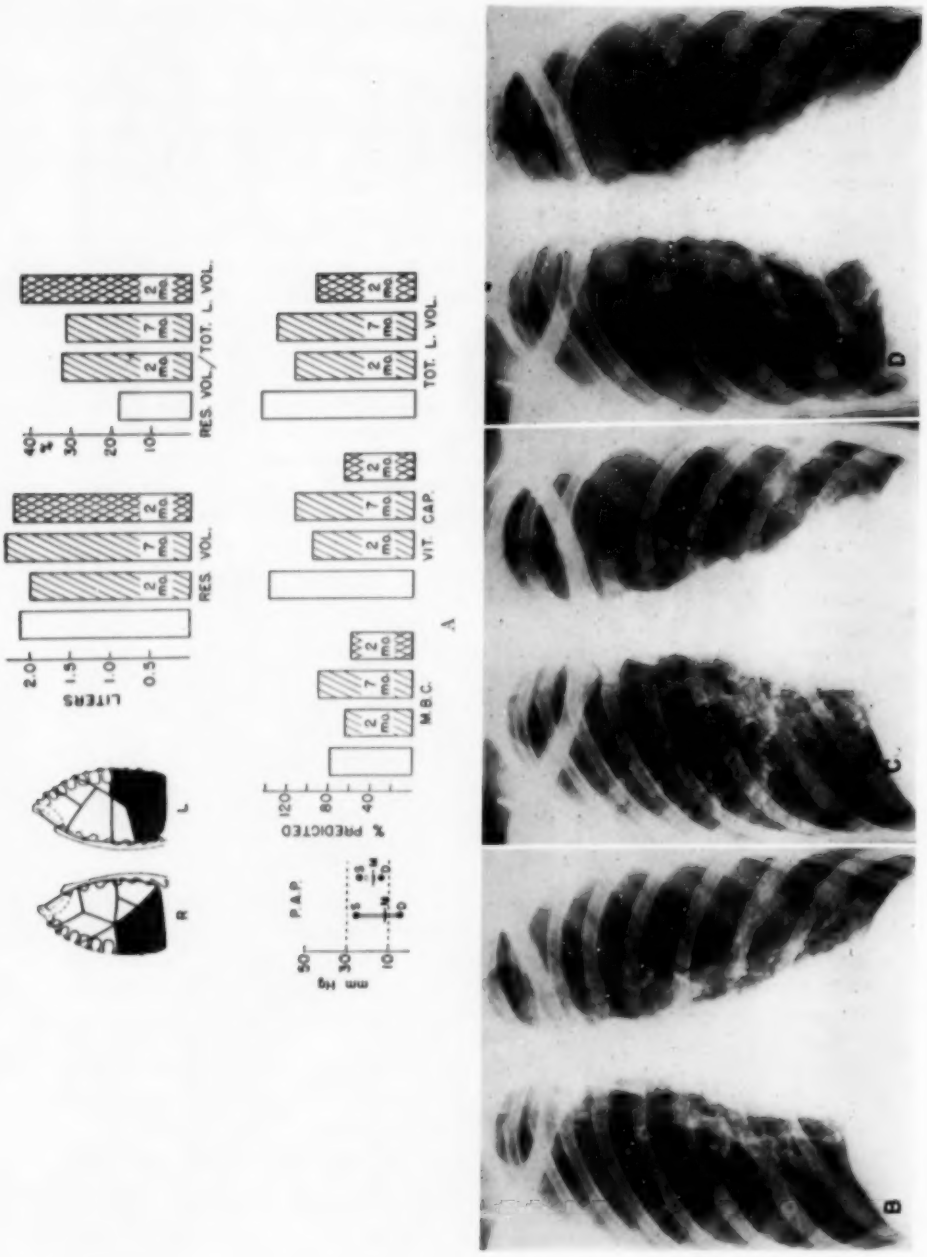
A
% PREDICTED
120
80
40
M.B.C.
2 mo.
7 mo.
2 mo.
VIT. CAP.
2 mo.
7 mo.
2 mo.
TOT. L. VOL.
2 mo.
7 mo.
2 mo.
RES. VOL.
2.0
1.5
1.0
0.5
LITERS
2 mo.
7 mo.
2 mo.
RES. VOL./TOT. L. VOL.
40
30
20
10
%
P.A.P.
50
30
10
mm Hg
L
R
B
C
D

FIG. 6 A-D

volume or functional residual volume attributable to surgery. Since vital capacity falls significantly in such patients, however, it is evident that the ratios residual volume/total lung volume and functional residual volume/total lung volume increase. Such an effect, however, should not place respiration at a disadvantage except under unusual circumstances. The fact that intrapulmonary mixing was unimpaired by resection is also borne out by the reduction in alveolar nitrogen consistently recorded.

Patients with bilateral disease tend to have elevated residual and functional residual volumes. Seven such patients were studied; 5 became normal following their first operation and 2 remained essentially unchanged. Two patients with bilateral disease who had normal residual volumes preoperatively and 3 additional patients who had normal values after their first operation showed the following results after their second operation: In 2 the residual volume remained essentially unchanged, in one it was augmented but normal, and in 2 the values for residual volume became abnormal. The last-named 2 patients showed progression of their "overdistention" within the period of study. One (Lab. #0027) was a 25-year-old man with resection of the right middle and lower lobes together with two segments of the left upper and three segments of the left lower lobes. The other (Lab. #0003) was a 46-year-old man (figures 5*A* and *B*) with resection of the right middle lobe, two segments of the left upper lobe, and three segments of the left lower lobe. A 21-year-old man (patient Lab. #0143), who had the same resection as the latter patient (Lab. #0003) plus the basal segments of the right lower lobe, was found to have a relatively normal volume of residual air.

In the presence of an elevated residual volume due to bilateral bronchiectasis, therefore, it is common to find a fall following the first operation. Moreover, some young patients demonstrate no striking abnormality even after an operation on the second side. Unless residual and functional residual volumes are reduced postoperatively, however, the amount of air present per quantity of lung tissue must increase. Constancy of residual volume, therefore, is insufficient to ensure normal inflation following resection; the demonstration that residual

FIG. 6*A*. Patient Lab. #0124. Age 23. Preoperative values indicated by clear bars. First operation: basal segments left lower lobe, inferior segment lingula. Second operation: basal segments right left lobe. Numbers indicate time of study following first (oblique hatching) and second (cross-hatching) operations. For roentgenograms, see figures 6*B*, *C*, and *D*.

Note: (*1*) normal pulmonary artery pressures after second operation; (*2*) effect of time on recovery of function following first operation; (*3*) progressive loss in maximum breathing capacity, vital capacity, and total lung volume with additional surgery; (*4*) relative constancy of residual volume; (*5*) stepwise increase in ratio of residual volume/total lung volume.

FIG. 6*B*. Patient Lab. #0124. Preoperative roentgenogram.

FIG. 6*C*. Patient Lab. #0124. Roentgenogram seven months after first (left) resection. Retained Lipiodol may be seen in both lung fields.

FIG. 6*D*. Patient Lab. #0124. Roentgenogram two months after second operation. The costophrenic sulci are obliterated; the right hemidiaphragm is elevated and flattened.

air does not rise strikingly after a bilateral procedure is merely a less unfavorable sign than an increase would be.

Finally, in regard to *complications*, the rewards of surgical skill and meticulous postoperative care are clearly measured in functional terms in the data (table 8) which compare the postoperative status of 13 patients who pursued an uneventful convalescence with that of 6 patients with equal resections (three to five segments) whose postoperative difficulties resulted in relative fixation of the ipsilateral diaphragm. In terms of vital capacity and maximum breathing capacity, the latter group approached the functional deficit exhibited by patients who have had extensive unilateral or bilateral resections (*see*, for example, figures 7*A* and *B*). The small residual air in these patients, however, can probably be attributed to fixation of the diaphragm in an elevated position consequent to a previous basal empyema.

In contrast to the correlation which this series of patients demonstrated between extent of disease and resection, on the one hand, and ventilatory status, on the other, is the lack of a similar relationship with respect to oxyhemoglobin saturation of arterial blood. As used in this analysis, saturation was a rather gross tool; perhaps correlations would have been clearer had greater finesse, such as the measurement of venous admixture, been applied. Nevertheless, the values suggest that deficiencies of arterial oxygen content are related to the type of lesion and not exclusively to its extent. Using contrast media to identify respiratory as well as vascular trees in autopsy specimens of bronchiectatic lung, Gobbel, Gordon, and Digman (35) have demonstrated the patency of vascular channels leading to affected, and presumably poorly ventilated, segments. Correspondingly, angiocardiograms performed upon 5 patients in this series showed normal vascular filling of bronchiectatic areas. To the extent that such shunts exist, one might account for a deficiency of arterial oxygenation or, in other words, a high venous admixture. Values for this measurement recorded for the 2 unoperated patients in table 13 may be accounted for in this manner. The low saturation of one patient (Lab. #0022) (figures 8*A* and *B*) can undoubtedly be explained on this basis. The premise is offered that the extent of ventilatory loss following operation is proportional to the size of the resection, whereas the quantity of venous admixture is not necessarily related to the extent of disease. If these postulates are true, that patient with a localized lesion and a large shunt in the diseased area can be expected to show the most dramatic benefit from surgical treatment.

At the other extreme are patients with extensive disease in whom the accumulation of perfusate from many poorly ventilated areas results in unsaturation (*see*, for example, figures 9*A* and *B*). In these, the ventilatory deficit which can be predicted to follow large bilateral resections must be weighed against the hope of symptomatic benefit, the uncertainty of improved oxygenation (8), and the probable control of clinically significant disease. Although none of the patients herein reported experienced pronounced respiratory insufficiency at the time of postoperative study, reports of such cases may be found in the literature (8, 28).

In distinction to the work of Gobbel and associates, the studies of Liebow,

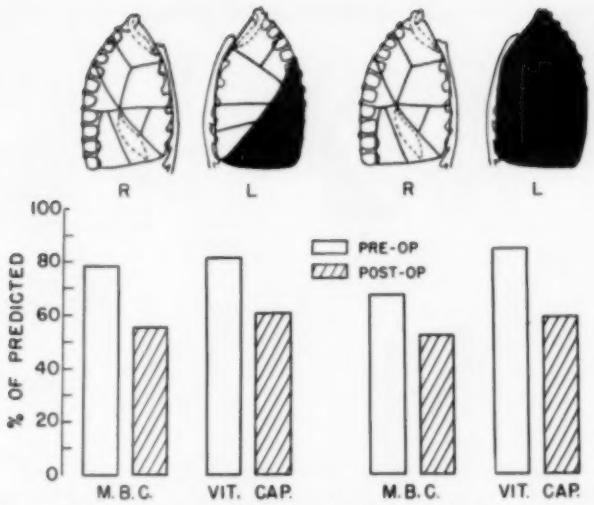

FIG. 7A. Patient Lab. #0040. Age 22. Excision of left lower lobe; phrenemphraxis at time of surgery (for roentgenogram, see figure 7B); atelectasis and mild empyema postoperatively. Patient Lab. #0027. Age 33. Left pneumonectomy.

Note: The postoperative maximum breathing capacity and vital capacity in these two patients with unequal resections is nearly identical.

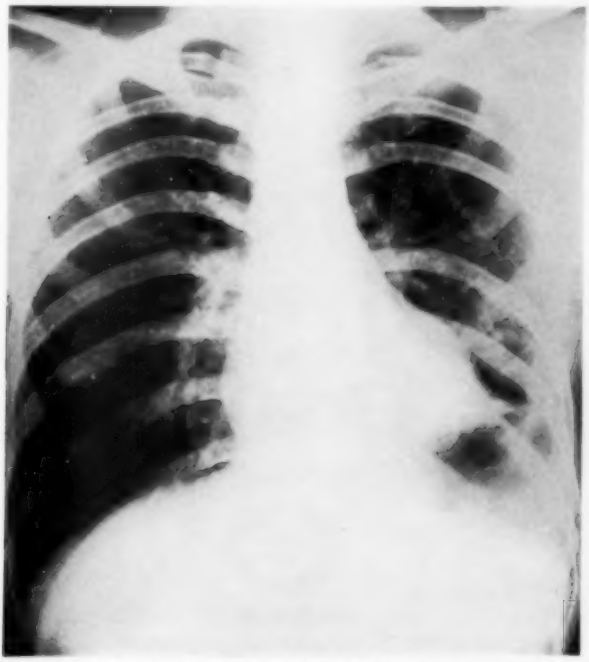

FIG. 7B. Patient Lab. #0040. Postoperative roentgenogram. Note elevation of left hemidiaphragm and pleural reaction at left base.

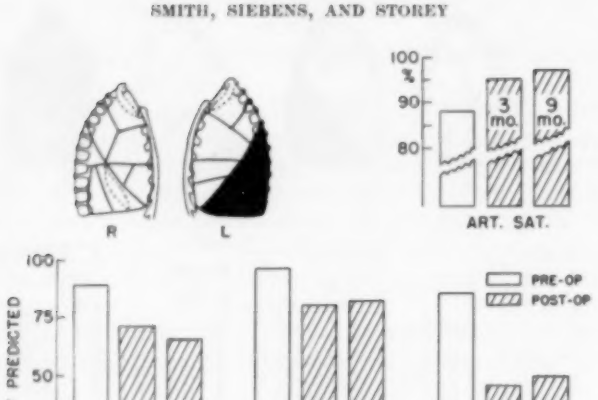

FIG. 8A. Patient Lab. #0022. Age 20. Resection of left lower lobe. For bronchogram, see figure 8B. Note excision of striking saccular bronchiectasis although reducing ventilatory function resulted in improved oxygenation of arterial blood.

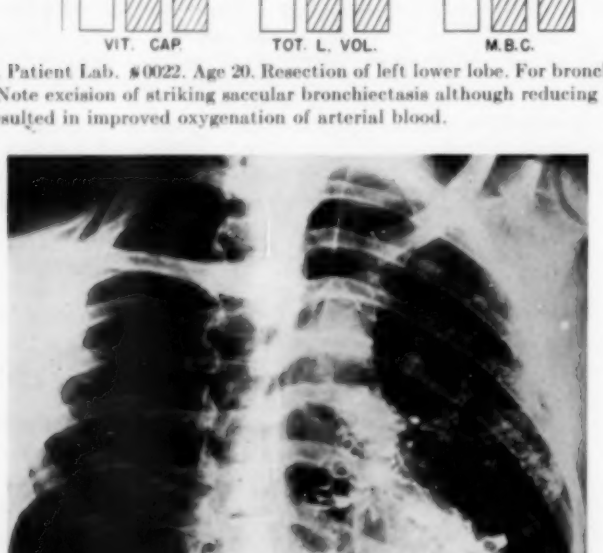

FIG. 8B. Patient Lab. #0022. Preoperative right anterior oblique bronchogram. Note striking saccular bronchiectasis confined to the left lower lobe.

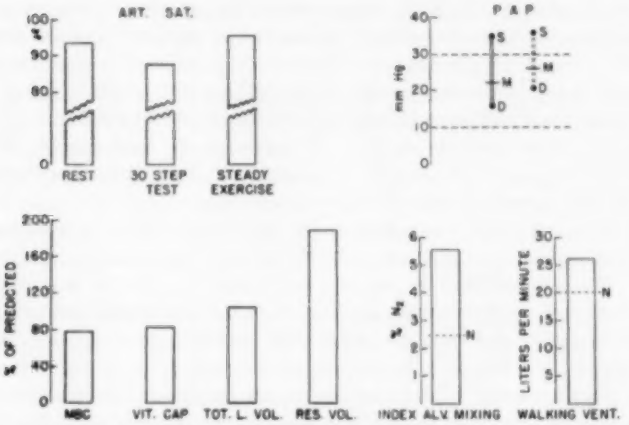

FIG. 9*A*. Patient Lab. #0360. Age 22. Bronchiectasis in right lower lobe, right middle lobe, and posterior segment of right upper lobe; left lower lobe, lingula, and anterior segment of left upper lobe. For bronchogram, see figure 9*B*.

Note: (*1*) borderline saturation at rest falls on 30-step test but rises to normal values on steady exercise; (*2*) residual volume, index of alveolar mixing, walking ventilation, and pulmonary artery pressures are elevated. Medical management was recommended in view of extent of disease, poor function, and elevation of pulmonary artery pressures.

FIG. 9*B*. Patient Lab. #0360. Bronchogram: note extensive bilateral cylindrical bronchiectasis.

Hales, and Lindskog (36) have demonstrated the presence of anastomoses between the bronchial and pulmonary circulation in patients with bronchiectasis. The structural basis for the delivery of considerable quantities of well-oxygenated blood from a high pressure system into the pulmonary vessels of bronchiectatic segments has, therefore, been indicated. The variability of saturation in patients with bronchiectasis may be explained in terms of the contributions from each of these vascular channels, for the oxygenation of pulmonary venous blood will reflect the relative magnitude of these two streams.

In addition to the effect just mentioned, the presence of anastomoses with the systemic circulation is also a factor which favors elevation of pulmonary artery pressure. The overinflation in patients with extensive disease and the hypoxia found in some of these persons may also be listed as possible contributory elements in the development of pressures such as those recorded in patient Lab. #0360 (figure 9*B*) (37, 38). Resection affects each of these three factors and imposes a fourth. On the one hand, it eliminates systemic pulmonary anastomoses and may improve saturation; on the other, it may increase overdistention and it does reduce the cross-sectional area through which the cardiac output must be forced. That the latter factor leaves its mark upon the pulmonary circulation in patients with pneumonectomies (39) and in animals following excision of lung (40, 41) has been established. The data from the present study provide suggestive evidence that there is a similar effect in patients who have had bilateral resections (table 13, figure 4). It is clear, therefore, that the hemodynamics of the lesser circulation must be critically considered in a thoughtful selection of patients for extensive bilateral resection.

SUMMARY

Cardiopulmonary function tests were performed upon 64 patients with bronchiectasis, 40 of whom were studied both before and after surgical treatment. Most postoperative studies were made less than six months after surgery.

Bronchiectasis was found to produce a ventilatory deficit proportional to the extent of the disease.

Operation was found to produce a further ventilatory loss proportional to the extent of resection. By statistical analysis, this loss was shown to be significantly greater in patients with resections of three or more segments than in patients with resections of two segments or less.

Statistical significance was attached to the ventilatory loss which follows the excision of little or no pulmonary tissue ("thoracotomy effect").

The development of complications inflicted significant additional loss upon postoperative ventilatory function.

Vital capacity and maximum breathing capacity were sensitive indices for detecting these trends.

An elevation of the ratio of residual volume/total lung volume commonly followed operation. This change usually reflected a fall in vital capacity rather than a significant increase in residual volume.

Although some preoperative patients had reduced oxyhemoglobin saturations

at rest or exercise, a relationship between this determination and the extent of the disease was not apparent. No patient had a "low" resting saturation following surgery.

These considerations indicate that the patient from whom the most dramatic postoperative functional result can be anticipated should have localized disease characterized by a large shunt.

In the presence of diffuse bilateral disease, resection was followed by a ventilatory deficit superimposed upon the pronounced impairment engendered by disease.

Oxygen content of arterial blood may be improved and pulmonary artery pressures may be moderately elevated postoperatively in patients with bilateral resections.

In view of the fact that available agents permit effective medical treatment of many patients with certain types and degrees of bronchiectasis and since both the adverse and beneficial effects of surgery upon the cardiorespiratory system may be reasonably well predicted, the choice of therapy for these patients should be made only after thoughtful functional evaluation.

SUMARIO

Estudio de la Función Cardiopulmonar Preoperatoriamente y Postoperatoriamente en los Enfermos de Bronquiectasia

Ejecutáronse pruebas de la función cardiopulmonar en 64 enfermos de bronquiectasia, estudiándose a 40 antes y después de tratamiento quirúrgico. La mayor parte de los estudios postoperatorios se hicieron menos de seis meses después de la cirugía.

Según se observó, la bronquiectasia producía un defícit ventilatorio proporcional a la extensión de la enfermedad.

La operación a su vez producía otra pérdida ventilatoria proporcional a la extensión de la resección. Conforme al análisis estadístico, esa pérdida era notablemente mayor cuando las resecciones comprendían tres o más segmentos que cuando comprendían dos segmentos o menos.

Reveló importancia estadística la insuficiencia ventilatoria consecutiva a la excisión de poco o de ningún tejido pulmonar ("efecto de la toracotomía").

La aparición de complicaciones impuso otra pérdida más significativa de la función ventilatoria postoperatoria.

La capacidad vital y la capacidad respiratoria máxima constituyeron índices sensibles para descubrir las tendencias mencionadas.

Por lo general, la operación fué seguida de elevación de la proporción del volumen residual/volumen pulmonar total. Esa alteración reflejó habitualmente una baja de la capacidad vital más bien que aumento importante del volumen residual.

Aunque algunos enfermos mostraron postoperatoriamente menores saturaciones de oxihemoglobina en descanso o en ejercicio, no se observó relación alguna entre esa determinación y la extensión de la enfermedad. Ningún enfermo mostró saturación "baba" en reposo después de la cirugía.

Las consideraciones anteriores indican que el enfermo en que cabe esperar el resultado funcional más dramático postoperatoriamente debe tener una enfermedad localizada caracterizada por una gran desviación.

Cuando existía afección bilateral difusa, la resección fué seguida de insuficiencia ventilatoria sobrepuesta a la pronunciada incapacidad engendrada por la dolencia.

En los enfermos que experimentan resecciones bilaterales, puede que, postoperatoriamente, mejore el contenido de oxígeno en la sangre arterial y que se eleven moderadamente las presiones en la arteria pulmonar.

En vista de que los agentes disponibles ya permiten administrar tratamiento médico eficaz a muchos enfermos con ciertas formas y grados de bronquiectasia y dado que ya cabe predecir con bastante certeza los efectos tanto adversos como beneficiosos de la cirugía sobre el aparato cardio-respiratorio, no debe elegirse la terapéutica para esos pacientes sino después de una juiciosa valuación funcional.

RESUME

Etude de la fonction cardio-pulmonaire préopératoire et post-opératoire de malades atteints de bronchiectasie

Des tests de la fonction cardio-pulmonaire ont été pratiqués chez 64 malades atteints de bronchiectasie, 40 d'entre eux furent étudiés avant et après le traitement chirurgical. La plupart des études post-opératories ont été faites moins de six mois après l'intervention.

On a découvert que la bronchiectasie produisait une perte de ventilation proportionnelle à l'étendue de l'affection.

L'intervention a révélé que la diminution du taux de ventilation augmentait proportionnellement à l'étendue de la résection. L'analyse statistique a permis de voir que cette réduction était significativement plus grande chez les malades ayant subi la résection de trois segments ou plus, que chez ceux ayant subi une résection de deux segments ou moins.

Une importance statistique était conférée à la perte subie par la fonction de ventilation qui succède à l'excision d'un fragment réduit de parenchyme pulmonaire ou à l'absence d'excision ("thoracotomy effect.")

Le développement de complications a infligé une perte additionnelle appréciable à la fonction de ventilation au stade post-opératoire.

La capacité vitale et la capacité respiratoire maxima constituaient des index très sensibles pour déceler ces tendances.

Une élévation du rapport volume-résiduel/volume pulmonaire total succédait habituellement à l'intervention. Cette modification reflétait habituellement une chûte de la capacité vitale plutôt qu'une augmentation significative du volume résiduel.

Bien que certains malades aient présenté avant l'opération une réduction de la saturation en oxyhémoglobine au repos ou à l'effort, une corrélation entre cette détermination et l'étendue de l'affection n'était pas apparente. La saturation au repos "basse" n'a été observée chez aucundes malades à la suite de l'intervention.

Ces considérations indiquent que le malade susceptible de présenter le résultat fonctionnel post-opératoire le plus saisissant doit être celui ayant une affection localisée caractérisée par un dérivation importante.

En présence d'une affection bilatérale diffuse, la résection était suivie d'un déficit de la ventilation qui s'ajoutait à l'insuffisance de fonction prononcée résultant de la maladie.

Après l'opération, il peut se produire une amélioration de la teneur en oxygène du sang artériel ainsi qu'une elévation modérée des tensions de l'artère pulmonaire chez les malades ayant subi des résections bilatérales.

Etant donné qu'on dispose d'agents permettant le traitement médical efficade de nombreux malades présentant certaines formes et divers degrés de bronchiectasie, et comme on peut raisonnablement prévoir les effets favorables ou défavorables de l'acte opératoire sur le système cardio-respiratoire, le choix du traitement pour ces malades ne doit être fait qu'après une évaluation fonctionnelle minutieuse.

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Most of the ventilatory studies, calculations, and chemical analyses were performed by trained hospital corpsmen, without whose skill and interest much of this work could not have been performed. Among these are the following: John Briggs, Kenneth Gorr, Richard Monsees, David Prior, Robert Rauf, and Richard Struts.

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TREATMENT OF CHRONIC PULMONARY EMPHYSEMA[1,2]

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INTRODUCTION

Chronic pulmonary emphysema can be defined as the diffuse, progressive, obstructive, and hypoxic type of chronic emphysema in which pathologic distention of alveoli has persisted for some time (1). It occurs with, or as a complication of, practically all pulmonary diseases, particularly severe bronchial asthma, bronchiectasis, serious pulmonary infection, the pneumoconioses, sarcoidosis, and tuberculosis. The common denominator is usually a diffuse chronic bronchitis. Chronic pulmonary emphysema is one of the most distressing of the diseases of the lung.

PHYSIOPATHOLOGY

The dynamic pressure relationships within the chest and between the intra- and extrathoracic spaces are essential to the normal airflow patterns of inspiration and expiration. Bronchial or bronchiolar obstruction disturbs these airflows. Normally, in expiration the cross-sectional area of the bronchi is decreased. When this decrease is markedly exaggerated, it diminishes expiratory airflow and prolongs the expiratory time. Increased resistance to expiration results in incomplete alveolar emptying or "trapping" of air in the alveoli (localized or generalized). This results in progressive overdistention of alveoli. Finally, interalveolar septa may rupture, giving rise to blebs and bullae.

The increased intra-alveolar pressure will compress the surrounding normal alveoli and the bronchioles, especially during forced expiration or cough (2). This has actually been observed bronchoscopically and has been explained on the basis of an increased alveolar volume without a corresponding increase in the cross-sectional area of the air passages. During expiration the intra-alveolar pressure rises above the intrabronchial pressure and compresses the air passages. This mechanism constitutes an expiratory check-valve on the terminal bronchioles (3). A vicious cycle is initiated, and further alveolar distention and alveolar damage follow.

The progressive increase in lung volume encroaches upon its surroundings; it depresses the diaphragms, and the lungs push into the mediastinum. As the alveoli enlarge and lose many of their septal walls (destruction of "alveolar membrane"), a decrease of alveolar-capillary contact (reduction in surface area)

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results in the face of an increased alveolar volume. A twofold disturbance in physiologic function now ensues:

1. Ventilation in and out of these alveoli, blebs, and bullae is irregular and inadequate. Part of the air does not come in contact with the capillary surface for gas exchange. This constitutes, in effect, an increased dead-space type of ventilation.
2. Since most of the air within these enlarged alveoli is stagnant, the blood will leave these alveoli without a significant decrease in its carbon dioxide content or an increase in its oxygen content. This blood, instead of becoming arterial, remains venous and re-enters the systemic circulation. This results in an increased venous admixture and is manifested by hypoxia (4).

As the disease progresses, the disturbances in pulmonary ventilation will be followed by hypoxia and later on by hypercapnia. Finally, cor pulmonale develops, and right-heart failure ensues as a terminal event. Pulmonary arterial hypertension of a chronic nature is the main disturbance which leads to cor pulmonale, cardiac hypertrophy, dilatation, and finally failure. This hypertension is due to a diminished pulmonary vascular bed secondary to actual destruction of alveolar capillaries and the effects of hypoxia. Polycythemia and hypervolemia also contribute to the pulmonary arterial hypertension (5).

SYMPTOMATOLOGY

Early manifestations consist of cough and dyspnea on exertion. The dyspnea may be caused by such acts of exertion as coughing, sneezing, or straining. The dyspnea is accompanied by hyperventilation. Subsequently, the dyspnea becomes progressively more severe, and bronchospastic crises, resembling a paroxysm of bronchial asthma, may occur.

There is a tendency for the cough to become more troublesome, more persistent and readily initiated by various nonspecific irritants: cold air, wind, fumes, dust, smoke, et cetera.

In the advanced stages of the disease, the above symptoms are more severe and, in addition, there is easy fatigability, dyspnea at rest, orthopnea, and cyanosis. There may be evidence of heart failure. The pulmonic second sound is usually accentuated and may be louder than the aortic second sound.

In this advanced stage of chronic pulmonary emphysema, the patient has a tendency to develop respiratory acidosis. This may occur spontaneously in the course of the disease or be induced by the inadvertent administration of high concentrations of oxygen or respiratory-depressing drugs. The patient may complain of headache, confusion, or irritability, and hypoventilation is usually noted. If the respiratory acidosis is allowed to progress, drowsiness, delirium, coma, and death follow. The basic defective mechanism which is responsible for this syndrome is inadequate alveolar ventilation with marked retention of carbon dioxide (6).

PULMONARY FUNCTION TESTS

Measurements of lung volume reveal that patients with chronic pulmonary emphysema have a decreased vital capacity as a rule, a small inspiratory capacity,

an enlarged functional residual capacity and residual volume, a slight increase of the timed vital capacity, and a significantly increased ratio of the residual volume to the total lung capacity.

Ventilation studies reveal serious ventilatory defects in the majority of patients. An increased resting ventilation, a decreased maximal breathing capacity, a markedly diminished ventilatory reserve, and an elevation of the index of intrapulmonary mixing are noted. Essentially similar findings were recorded in the patients with chronic bronchial asthma (7).

Treatment of the patients with either intravenous aminophylline or a potent bronchodilator aerosol demonstrates that many of the observed defects are reversible to various degrees. Changes effected in a group of patients with intravenous aminophylline and bronchodilator aerosols, respectively, were: vital capacity, plus 21 and plus 22 per cent; residual volume, minus 9 and minus 8 per cent; residual volume/total lung capacity ratio, minus 8.5 and minus 7.6 per cent; maximal breathing capacity, plus 25 and plus 59 per cent; index of intrapulmonary mixing, minus 39 and minus 34 per cent (1).

The arterial blood oxygen, carbon dioxide, and pH may be normal in the patients with mild pulmonary emphysema. As the disease progresses, hypoxia will be present after exercise but, later on, at rest as well. Inasmuch as carbon dioxide has a much greater diffusibility than oxygen and is easily blown off, carbon dioxide retention will occur late in the disease after severe hypoxia has been present for some time. A normal pH can be maintained for a long time by compensatory mechanisms, but eventually respiratory acidosis develops.

In the advanced stages of chronic pulmonary emphysema, cardiac catheterization may reveal an elevated pulmonary arterial pressure and a considerably increased cardiac output (8, 9).

TREATMENT

The treatment of chronic pulmonary emphysema will be discussed according to the following categories:

Symptomatic treatment
Bronchodilators
Antimicrobial drugs
Enzyme aerosols
Humidification (water, detergents)
Oxygen therapy
Corticotropin or cortisone
Breathing exercises
Pneumoperitoneum
Mechanical respiration
Pulmono-cardiac complications

The patient should be informed about the hazards of upper respiratory infections and overexertion. Recovery from these episodes is slow, but fortunately most of the physiologic changes are reversible to various degrees with vigorous treatment.

Symptomatic Treatment

The various factors responsible—occupational, infectious, or allergic—should be analyzed in every case. Specific measures, e.g., hyposensitization, although too often disappointing, should be attempted.

The bronchitic cough is one of the most troublesome manifestations and may actually serve as the trigger mechanism for more extensive bronchiolar spasm and alveolar disintegration. The expectorant antihistaminic preparations, such as an oral solution of diphenhydramine hydrochloride (Benylin compound) or tripelennamine hydrochloride (Pyribenzamine expectorant), are well tolerated by many patients. Theophylline ethylenediamine plus diphenhydramine hydrochloride (Hydrillin compound) have the advantages of aminophylline in combination with diphenhydramine hydrochloride (Benadryl). The writers have recently employed na-ethane disulfonate (Toryn), 10 mg. every six hours, in syrup or tablet form. It is an effective antitussive agent with anticholinergic properties primarily, but is essentially free of atropine-like effects. Na-ethane disulfonate has been well tolerated and appears to have a sedative effect on the bronchioles. The ineffective cough was greatly improved in many patients. Iodides may be taken with these expectorants to promote more adequate "bronchial catharsis" in the more severe chronic form of bronchitis.

The smaller doses of ephedrine sulfate (up to 22.5 mg.) may be useful in mild cases, particularly when combined with effective doses of aminophylline. Many observers have found methoxyphenamine hydrochloride (Orthoxine) as effective as ephedrine, with fewer side reactions. There are many oral medications combining aminophylline with ephedrine for the relief or prevention of mild but chronic bronchoconstriction. The difficulty with most of these preparations resides in their side reactions, when using doses of aminophylline which are large enough to achieve therapeutic results. The addition of antinausea factors (local and central) to aminophylline has made it possible to administer effective larger doses of aminophylline with or without ephedrine or a barbiturate (Dainites and Cardalin). Larger aminophylline blood concentrations (more than 0.5 mg. per cent) may be necessary for more persistent bronchospasm, particularly when associated with chronic bronchial asthma. These concentrations can be obtained by the use of aminophylline solutions given by rectal or intravenous administration of calcium theophyllinate (Calphyllin) solution by rectal instillation. The writers have found aerosols of aminophylline dust or liquid of no significant value.

Bronchodilators

Aerosols of sympathomimetic drugs, such as racemic epinephrine hydrochloride (Vaponefrin) and isopropylarterenol hydrochloride (Isuprel), have proved to be of great value for the relaxation of bronchospasm (10, 14). As little as approximately 0.05 to 0.10 cc., nebulized by three to six compressions of a hand bulb, may abort or relieve a mild bronchospastic episode. More severe bronchospasm may require 0.5 to 1.0 cc., nebulized by continuous flows of oxygen, helium-oxygen, or by air pump. The following mixture has been found of value: 0.5 cc. of 2.25 per cent of racemic epinephrine hydrochloride, 0.5 cc. of 1 per cent of phenylephrine hydrochloride (Neosynephrin, broncho-vasoconstrictor), and 0.5 cc. of an aqueous solution containing 0.125 per cent of oxyethylated tertiary octylphenol-formaldehyde polymer (Alevaire, detergent). This treatment generally requires ten to fifteen minutes with 4 liters per minute flow. A Y-tube or

simple button-like opening into the oxygen or air feed line allows interruption of aerosol production during expiration. The aerosols may be introduced along with intermittent positive pressure breathing in inspiration (IPPB/I) with the Bennett valve (11, 12, 13), thus obtaining the physiologic advantage of driving the therapeutic agent through partially obstructed airways. A useless cough is often converted to a productive one by effective bronchodilation therapy.

Antimicrobial Drugs

The choice of the antimicrobial drug (penicillin, streptomycin, or oxytetracycline (Terramycin)) depends on the predominating organisms, their drug susceptibility, and the patient's tolerance for the drug itself. Penicillin is generally the primary drug employed for gram-positive organisms; streptomycin or oxytetracycline may be added or used alone if gram-negative bacteria are also present or emerge, or if bronchorrhea persists. Crystalline penicillin is given in doses of 50,000 to 100,000 units; streptomycin, in doses of 0.25 gm., and oxytetracycline in doses of 100 mg., four times daily. A course of therapy may range from one to six weeks.

The antimicrobial aerosols may be combined with equal amounts, e.g., 0.5 cc. of each, of a bronchodilator preparation and a detergent. One-half centimeter of phenylephrine hydrochloride (1 per cent) may be added to an equal amount of the bronchodilator for better relief of bronchial edema.

Most of the writers' patients have been able to raise sputum more easily while receiving these aerosols. The hazard of local or generalized allergic reaction to penicillin aerosol in patients with underlying bronchial asthma must never be overlooked. Bronchoscopic lavage may greatly enhance the subsequent value of bronchodilator and antimicrobial aerosols in patients with associated bronchiectasis.

Supplemental parenteral penicillin, streptomycin, or one of the broad-spectrum antimicrobials (the tetracyclines or chloramphenicol) should be employed if there is evidence of a severe respiratory tract infection. A hydriodide ester of penicillin (Neo-Penil), given intramuscularly in doses of 500,000 units every twelve hours, produces essentially low blood concentrations with effective concentrations in the sputum (15). Evidence from this and other laboratories (22) would indicate that it is a more effective form of penicillin in patients with chronic pulmonary emphysema and bronchopulmonary infection. The recent incidence of serious reactions reported from this hydriodide ester of penicillin is probably no greater than from the use of procaine penicillin.

Paranasal sinus disease may be responsible for reinfection and the recurrence of cough and wheezing respirations. An irreparable sinobronchitic syndrome often follows in its wake. Most of these patients have underlying allergy. The writers have found a compound of paradrine hydrochloride (Drilitol) quite helpful, especially when administered three or four times daily with a nebulizer (Vaponefrin), using nasal tips, employing air or oxygen. With evidence of frank purulent infection, 100,000 units of penicillin should be added to 1 cc. of 1 per cent phenylephrine hydrochloride (Neosynephrine) and 1 cc. of 1 per cent

tripelennamine hydrochloride (Pyribenzamine), and nasal aerosols administered with the same technique. These agents are generally well tolerated nasally. Postnasal drip with secondary cough is reduced, nasal patency is restored, and more restful sleep may follow.

Enzyme Aerosols

In the presence of bronchial infection, bronchiectasis, or tenacious purulent secretions, the use of enzymes to attack the pus, e. g., pancreatic desoxyribonuclease (Pancreatic Dornase) is indicated (16). It has proved to be more efficacious in clearing bronchial infection of a chronic nature than the use of antimicrobials by aerosol, or parenterally, alone. Pancreatic desoxyribonuclease, dissolved in a special diluent, is administered by aerosol in doses of 50,000 to 100,000 units, one to three times daily for several days to several weeks. It is used in addition to, not instead of, antimicrobial therapy.

Humidification

In the treatment of a troublesome bronchitis or bronchiolitis with inspissated mucus, humidification therapy may be employed before attempting aerosols of pancreatic desoxyribonuclease (17).

Satisfactory humidification can be obtained with cold water or, preferably, with aerosols of a nontoxic detergent (Alevaire). The writers have found the "Neb*E*Lizer"[5] apparatus most practicable and convenient for prolonged nebulization of cold water vapor or detergent. This apparatus (17) produces a continuous fine fog of water or detergent, originating from the attached 500 cc. reservoir of solution. A single oxygen tank with flows of 12 liters per minute ensures continuous nebulization, without "rain outs" of large particles onto the patient. The patient's head is placed in the enclosing oxygen tent, e.g., the Permatent Croup Unit.[5] Water vapor saturation of more than 90 per cent and temperatures below 70°F. can be quickly obtained and readily maintained within the tent with this technique when water is employed. The Neb*E*Lizer can be attached directly to the ABC plastic Oxygen Face Tent[5] or O.E.M.[6] meter mask for home use.

Oxygen Therapy

Carbon dioxide intoxication syndrome: The sudden administration of high concentrations of oxygen in an attempt to relieve dyspnea, hypoxia, and cyanosis in patients with chronic pulmonary emphysema and pulmonary heart disease may be followed by the distressing symptoms of the so-called *carbon dioxide intoxication syndrome* (1). In these patients the medullary respiratory centers appear to have lost their sensitivity to the pCO_2 stimulus for respiration (centrogenic drive). Hence the chemo-reflex drive for respiration, the hypoxic stimulus from the sensory nerve endings in the carotid and aortic bodies, has to assume the chief responsibility for maintaining respiration in these patients. The sudden injudicious removal of this hypoxic stimulus may be followed by a breakdown in

[5] Manufactured by Eliot Medical Plastics, Inc., Lynn, Massachusetts.
[6] Manufactured by O. E. M. Corporation, East Norwalk, Connecticut.

the homeostatic mechanisms sustaining respiration, and further hypoventilation may ensue.

The carbon dioxide retention usually brings about a compensatory increase in the alkali reserve (metabolic alkalosis) and a fall in serum chlorides and increase in urine chlorides. Greater increase in the arterial pCO_2 and content may follow, and ultimately respiratory acidosis, with a drop in arterial pH. These factors appear primarily responsible for producing weakness, headache, air hunger, neurologic manifestations, drowsiness, coma, delirium, and death, which may develop progressively under such conditions.

This troublesome syndrome should not occur if one does not further depress respiration by the use of the respiratory depressing drugs (morphine, barbiturates, anesthetic agents) and if the sudden administration of high concentrations of oxygen to the chronically hypoxic patient is avoided.

Should respiratory depression occur, especially if caused by the administration of one of the opiate respiratory depressing drugs, intravenous *n*-allylnormorphine hydrochloride (Nalline) is the antagonist of choice (18, 19). Five to ten milligrams injected intravenously followed by a slow drip of 10 mg. of Nalline in 1,000 cc. of glucose in water will, as a rule, increase ventilation promptly.

A carefully graded program of oxygen therapy should be employed, consisting of daily increases in concentrations at the beginning of therapy and a gradual daily reduction toward its cessation. The acutely ill patient who needs oxygen should be treated by nasal catheter with humidified oxygen. At the outset, one should employ flows of 1 liter per minute. The flows may be increased 1 liter daily until 6 liters per minute flows of oxygen are obtained (6). A concentration of 38 per cent oxygen in the inspired air can be obtained at this flow. Some variations in the flow rates may be necessary from time to time.

Absence of carbon dioxide intoxication: For the routine management of chronic pulmonary emphysema, wherein oxygen is necessary at times and there is no evidence of marked increase in pCO_2, e.g., in acute respiratory tract infections and during troublesome bouts of bronchoconstriction, oxygen may be ideally administered with the ABC Plastic Oxygen Face Tent. The undesirable features of the nasopharyngeal catheter and of the more complex rubber face masks and oxygen tents are eliminated with this tent which is designed to administer oxygen in adequate concentrations for either brief or prolonged periods. The tent fits comfortably over the lower portion of the patient's face and opens widely at the forehead for easy egress of exhaled gases and vapors. Forehead and head straps ensure its stability. Humidified oxygen enters the face tent through a showerhead dispersal system. With oxygen flows of 6 liters per minute, average concentrations were obtained in the inspired air of 52.57 per cent oxygen, and the carbon dioxide was kept below 1 per cent (10).

Various types of enclosing tents have been devised for administration of oxygen to patients who cannot tolerate any type of face-fitting oxygen mask apparatus. We have found the Eliot Permatent capable of withstanding more than the average hospital abuse. It is constructed of a clear, heavy-gauge, durable vinyl plastic. Adequate zippered entrances permit easy access to the safely tilt-

able ice-tray compartment or to the patient. An adjustable neck collar comfortably encloses the patient's head. Two front portholes are present for the egress of carbon dioxide. The Neb*EL*izer can be attached to one of the portholes for the admission of cold water vapor, or aerosols of detergents, antimicrobials, or bronchodilators. The oxygen concentrations ranged from 50 to 70 per cent and the carbon dioxide accumulations have been consistently below 1 per cent when 10 to 14 liters per minute flow of oxygen was employed.

Corticotropin or Cortisone

The idea is appealing that irreversible fibrous changes following inflammatory pulmonary lesions can be prevented by the periodic use of corticotropin or cortisone, but it has not been substantiated (1, 20).

Patients with underlying hypersensitivity disorders of the lung, e.g., intractable bronchial asthma or periarteritis nodosa, should be given a trial with corticotropin therapy when a reversal of physiologic function has not occurred after adequate therapy. This trial should be made even in the presence of chronic cor pulmonale. It should be kept in mind that the dominant defect, *hypoxia*, is responsible for the chronic cor pulmonale and associated changes. When improvement of hypoxia does not follow treatment with bronchodilators, aminophylline, the use of intermittent positive pressure breathing, and proper concentrations of oxygen, then the rapid remission from the intractable bronchoconstriction made possible by corticotropin or cortisone should be attempted.

The presence of heart failure due to chronic cor pulmonale need not absolutely contraindicate the use of corticotropin or cortisone, provided all of the physiologic principles are followed for the management of such failure. Temporary aggravation of failure, demonstrated by hepatic enlargement or leg edema, occasionally may appear. Nevertheless, relief from the effects of acute hypoxia superimposed on chronic hypoxia more than offsets the hazards of further heart failure. After corticotropin therapy, still greater improvement generally follows the use of digitalis, mercurials, and venesections.

During the acute phase, treatment is begun with corticotropin intravenously in order to effect rapid improvement. Thirty milligrams of corticotropin in 2 or 3 liters of glucose in water are given for a twenty-four-hour period by slow continuous intravenous drip (30 drops per minute flow). After two or three days, the treatment is changed to maintenance corticotropin (Acthar Gel), 40 units once daily. Gradually this is decreased to 20 units daily. At the conclusion of a course of therapy of one to two weeks, the patient is given oral cortisone for five to seven days. The latter is gradually omitted. Variations in this schedule are often necessary.

Breathing Exercises; Abdominal Supports

Both active and passive breathing exercises may improve the ventilatory efficiency (21). Barach and his associates recently emphasized the importance of developing diaphragmatic breathing by special training and daily practice (22). The patient is taught to lower the diaphragm, manifested by protrusion of the

abdomen during inspiration, and to press with both hands below the umbilicus inward and upward during the latter third of expiration. These procedures tend to restore the lost diaphragmatic excursions. The expiratory phase may be carried out for the sick patient passively and may help in eliminating trapped air. During these exercises the lips may also be kept pursed in expiration.

Barach and his associates suggest practicing this at first lying down, with one hand on the abdomen and one on the chest; the patient should attempt to see that the abdomen protrudes forward during inspiration, with little or no chest movement. After two minutes' trial, the same exercise should be tried sitting up, and then walking. Some patients learn this procedure quickly, and the movements soon become automatic. Others, particularly patients with flat abdomens and military bearing, have considerable trouble with the same procedures.

The present writers generally advocate breathing exercises designed to improve the spine and chest relationships, as well as diaphragmatic function, along with abdominal belts and skeletal support (orthopedic braces) when indicated; for example, for kyphoscoliosis. There are several types of emphysema belts, e.g., Gordon 2-band belt, Camp's, Spencer's, et cetera, to give the abdominal compression necessary to elevate the diaphragm to the level of expiration. These should be worn during the day only, and they are very useful.

A definite routine will be found more helpful than the occasional use of these procedures. The patients are instructed to take three to six inhalations of Vaponefrin upon arising and one hour before lunch, supper, and bedtime. This is followed by rhythmic deep-breathing exercises. After these exercises, the diaphragmatic breathing exercises previously described are performed. When possible, both of these exercise procedures should be repeated six to twelve times. Training should be encouraged. Fatigue should be avoided. A skilled and interested physiotherapist may be quite helpful. In cooperative patients the results are worth the effort. Exercises should stop in time for a fifteen- to thirty-minute rest period before each meal.

Pneumoperitoneum

Several groups of investigators have cited the usefulness of pneumoperitoneum, (23, 24). In many patients, the cough becomes more productive, less dyspnea is noted, and tolerance to mild exercise increases following induction of pneumoperitoneum. Improvement in appetite and weight gain may be noted. Such patients rest and sleep better.

Beck and co-workers (25) recently utilized the venous pressure as a guide for pneumoperitoneum therapy. A drop or no noticeable change in the venous pressure was considered a good indication for the effectiveness of pneumoperitoneum.

The indications for pneumoperitoneum therapy can be centered about the following principles (1):

> The restoration or improvement of the dynamic function of the diaphragm is the main object. The smallest amount of air necessary to restore the diaphragm to its normal position should be employed, in contrast to therapy in pulmonary tuber-

culosis in which lung rest is the primary aim. When successful elevation of the diaphragm with adequate motions has occurred, as determined by fluoroscopic control, refills are given at greater intervals.

Some degree of pulmonary reserve should be present before starting pneumoperitoneum.

The extent of active bronchoconstriction should be minimal. Maximum improvement with bronchodilator aerosols and clearance of infection with antimicrobials should be effected prior to instituting pneumoperitoneum therapy. Therapeutic failures are often due to neglect of these factors of bronchoconstriction and infection.

Complete evaluation of the anatomic integrity of the diaphragm (atrophic changes and presence of adhesions) should be made by fluoroscopy and roentgenographic studies.

When the syndrome of carbon dioxide retention with respiratory acidosis occurs and remains unrelieved by adequate intermittent positive pressure therapy with 40 per cent oxygen, or *adequate* movements of the chest cage and diaphragm do not follow respirator chamber treatment, immediate pneumoperitoneum, using large amounts of air, should be instituted. This may prove life-saving.

Mechanical Respiration

If the complete carbon dioxide intoxication syndrome appears, characterized by hypoventilation, respiratory acidosis, severe carbon dioxide retention, and the comatose state, mechanical respiration employing mask or chamber units may indeed have life-saving value (26).

Positive pressures should then be employed to maintain adequate ventilation and still safely provide adequate oxygen concentrations. The intermittent type supplies the gas mixture under positive pressure in either the inspiratory or expiratory cycle, usually through a mask device. There are several types of mask apparatus which supply intermittent positive pressure breathing in inspiration. The more commonly used ones are the Bennett, M.S.A., and Emerson units.

The writers have found the Bennett-type[7] cycling valve more satisfactory for administering positive pressure breathing, especially when combined with the attached nebulizer for administering bronchodilator aerosols (13). The patient completely controls the cycling of the valve by his own respiratory rhythm. An active inflation of the lungs occurs during inspiration under positive pressure from the cycling valve. The rapid release of pressure at the start of expiration is followed by a high velocity expiratory gas flow. This, combined with the release of bronchoconstriction which follows the simultaneous inhalation of bronchodilator aerosols, promotes better bronchial drainage. The period of temporary hyperventilation helps to eliminate the excess blood carbon dioxide. The writers have employed pressures of 10 to 20 cm. of water with mixtures of air and oxygen, depending upon the underlying causes for respiratory failure. When necessary, the apparatus can be manually operated as a controlled resuscitation valve by simple fingertip rhythmic cycling.

Positive pressure breathing in expiration (0 to 4 cm. of water) may be obtained with the O.E.M. Meter Mask (6). The patient sets up a gentle positive pressure

[7] Manufactured by V. Ray Bennett and Associates, Los Angeles, California.

in expiration by blowing the expired air through the narrowed orifices of the metering disk.

With marked slowing of respiration, the Drinker, Emerson, or Collins type of tank respirator may be used to give artificial respiration (26), with oxygen therapy provided by a catheter, face tent, or a Bennett-type cycling valve. The major problem lies in the difficulty in synchronizing the patient's respirations with the cycle of the respirator.

The patient who has secretions accumulated in the tracheobronchial tree, especially when his cough is weak and ineffective, requires mechanical exsufflation with negative pressure (E.W.N.P.), Barach's suggested form for "artificial coughing" (27, 28). This can be accomplished with the Eliot Exsufflator or the O.E.M. Cofflator units,[8] which create positive pressure on inspiration and negative pressure on expiration (28, 29). The change-over from positive to negative pressure is instantaneous so that a rapid expiratory flow rate is achieved. During this expiratory negative phase, the physiologic effects of a vigorous cough are generally accomplished. Positive-negative pressure breathing is safer than inspiratory positive pressure breathing alone in patients with circulatory inadequacy or in peripheral circulatory collapse. The mean intrapulmonary pressure throughout the cycle was close to the baseline atmospheric pressure (29). The negative expiratory-phase pressure helps to reconstitute the venous gradient and cardiac output as well as prevent a further drop in blood pressure, which may follow positive pressure on inspiration alone in patients with circulatory inadequacy.

Pulmono-Cardiac Complications

In the seriously ill patient, hypoxia becomes more pronounced with repeated bouts of respiratory infection or bronchospasm. As the homeostatic mechanisms are broken down, pulmono-cardiac changes appear. Cyanosis, clubbing, polycythemia, hypervolemia, increased cardiac output, and dilatation of the right ventricle may follow. Pulmonary hyperventilation occurs, inasmuch as the increased blood flow through the lungs from the increased cardiac output cannot be handled by distending the already reduced pulmonary vascular bed. The pulmonary hypertension may lead directly to right ventricular hypertrophy. Subsequent heart failure awaits the next trigger mechanism (30).

The management of this seriously ill group of patients warrants more optimism than was generally felt previously, if one remembers that the physiologic changes described above are largely reversible, although only temporarily. The basic therapy should center about relief of hypoxia, relief of bronchoconstriction, and management of infection.

The hypervolemia must be overcome by *repeated phlebotomies* of 250 to 350 cc. each. The clinical evidence of venous plethora (fullness in the head, et cetera), the imminence of heart failure, and the hematocrit level (45 per cent) should be the guides for venesection. The pulmonary artery pressure may be lowered

[8] Eliot Exsufflator manufactured by Eliot Medical Plastics, Inc., Lynn, Massachusetts, and Cofflator by the O. E. M. Corporation, East Norwalk, Connecticut.

to normal levels following venesection. The periodic use of *mercurial diuretics* combined with *phlebotomies* may be of great value, even in the absence of clinical evidence of frank right-sided heart failure. The serum chlorides should be watched, for they may be lowered in the group with metabolic alkalosis and low serum chlorides, compensatory to the elevation of the pCO_2, especially in patients on a low salt regimen.

Digitalis should be employed when there is evidence of right ventricular failure. The indication for its use in the presence of failure exists regardless of considerations of high or low cardiac outputs. In addition to digitalization, salt restriction and ammonium chloride should also be used in the presence of right-sided heart failure.

SUMMARY

Correlation of certain phases of management of the patient with chronic pulmonary emphysema with the knowledge of its physiopathology was attempted. The basic defects present in the patient with chronic pulmonary emphysema were demonstrated by means of pulmonary function studies. Continuous preventive measures to control and improve these abnormal findings should be employed.

The experiences of the present writers with several therapeutic measures in the treatment of chronic pulmonary emphysema and complicating manifestations were described, namely: antihistaminics, aminophylline, expectorant mixtures, antimicrobial agents, aerosols of bronchodilators, water, pancreatic desoxyribonuclease (Pancreatic Dornase) and a detergent (Alevaire), corticotropin and cortisone; and the use of venesection, digitalis, and the mercurials.

The general principles were outlined for the use of oxygen, intermittent positive pressure breathing in inspiration (IPPB/I), and continuous aerosol therapy. The combined use of bronchodilator aerosols with IPPB/I was described for the routine treatment of chronic pulmonary emphysema. The use of alternating positive-negative pressure breathing (exsufflation) has proved of considerable value for the evacuation of bronchial secretions when other therapeutic agents have failed.

The hazard of the carbon dioxide intoxication syndrome and respiratory acidosis is always present in patients with chronic hypoxia secondary to chronic pulmonary emphysema or chronic pulmonary heart disease, particularly if respiratory-depressing drugs are administered preceding or along with the high concentration of oxygen. The prevention and management of respiratory acidosis was discussed.

The principal indications and use of breathing exercises, pneumoperitoneum therapy, and various forms of mechanical breathing were presented.

SUMARIO

Fisiopatología y Tratamiento del Enfisema Pulmonar Crónico

Tratando de correlacionar ciertas fases de la asistencia del enfermo que tiene enfisema pulmonar crónico con nuestros conocimientos de la fisiopatología del último, pusiéronse

de manifiesto los defectos básicos que muestra el enfermo por medio de estudios de la función pulmonar. Hay que emplear continuas medidas preventivas para dominar y mejorar esos hallazgos anómalos.

Descríbense las observaciones de los AA. acerca de varias medidas utilizadas en el tratamiento del enfisema pulmonar crónico y de sus complicaciones, comprendiendo: antihistamínicos; aminofilina; mezclas expectorantes; antibióticos; aerosoles de broncodilatadores, desoxirribonucleasa pancreática hídrica (Dornasa Pancreática) y una solución acuosa que contenía 0.125 por ciento de un polímero de octilfenolformaldehído terciario oxietilado (Alevaire); corticotropina (ACTH) y acetato de cortisona; y empleo de la flebotomía, la digital y los mercuriales.

Bosquéjanse los principios generales del uso del oxígeno, de la respiración intermitente a presión positiva en la inspiración (RPPI/I) y la aerosoloterapia continua. Descríbese el uso combinado de los aerosoles de broncodilatadores con la RPPI/I para el tratamiento corriente del enfisema pulmonar crónico. El empleo de la respiración a presión negativa alternante (exsuflación) ha resultado de mucho valor para la evacuación de las secreciones bronquiales cuando fracasan otros agentes terapéuticos.

Hay siempre riesgo de que se presenten el síndrome de la intoxicación por bióxido de carbono y acidosis respiratoria en los enfermos que tienen hipoxia crónica secundaria a enfisema pulmonar crónico o cardiopatía pulmonar crónica, en particular si administran medicamentos que deprimen la respiración antes de una alta concentración de oxígeno o junto con ésta. Discútense la prevención y la asistencia de la acidosis respiratoria.

Repásanse las principales indicaciones y el uso de los ejercicios respiratorios, del neumoperitoneo terapéutico y de varias formas de respiración mecánica.

RESUME

Physiopathologie et traitement de l'emphysème pulmonaire chronique

Les auteurs ont tenté d'établir une corrélation entre certaines phases du traitement du malade atteint d'emphysème chronique et les données de la physiologie pathologique de cette affection. Les anomalies fondamentales présentes chez le malade atteint d'emphysème pulmonaire chronique ont été démontrées par l'étude de la fonction pulmonaire. Des mesures prophylactiques pour combattre et améliorer ces conditions anormales devront être appliquées.

La thérapeutique effectuée par ces auteurs dans le traitement de l'emphysème pulmonaire chronique et de ses complications est décrite. Les médications utilisées étaient suivantes: antihistaminiques; aminophylline; préparations expectorantes; agents antibiotiques; aérosols et broncho-dilatateurs, désoxyribonucléase pancréatique en solution aqueuse (Dornase pancréatique), solution agueuse á 0.125% d'un polymère de octylphénolformaldéhyde oxyéthylé tertiaire (Alevaire); corticotrophine (ACTH) et acétate de cortisone; la phlébotomie, la digitale et les mercuriaux étaient également utilises.

Les auteurs indiquent brièvement les principles généraux de l'emploi de l'oxygène, de la respiration sous pression positive intermittente dans l'inspiration (IPPB/1) et l'aérosolthérapie continue. L'emploi combiné d'aérosols bronchodilatateurs et de l'IPPB/1 comme traitement routinier de l'emphysème pulmonaire chronique est décrit. La méthode de la respiration dans un respirateur où les pressions positives et négatives sont alternée (exufflation) a fait preuve d'une valeur considérable pour l'évacuation des sécrétions bronchiques après échec des autres moyens thérapeutiques.

Le syndrome de l'intoxication par l'anhydride carbonique et l'acidose respiratoire est toujours à redouter chez les malades affectés d'hypoxémie chronique secondaire à l'emphysème pulmonaire chronique ou aux affections cardiopulmonaires chroniques, en particulier lorsque des médicaments dépresseurs de la respiration sont administrés avant ou en même temps que l'oxygène à haute concentration. La prévention et le traitement de l'acidose d'origine respiratoire sont c'ommentés.

Les indications principales et l'utilisation des exercices respiratoires classiques, du

traitement par le pneumopéritoine, et divers procédés mécaniques d'exercice de la respiration sont passés en revue.

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THE AFTER-HISTORY OF PULMONARY TUBERCULOSIS[1]

II. Thoracoplasty: Ten-Year Follow-Up

RICHMOND DOUGLASS AND EDWARD B. BOSWORTH

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INTRODUCTION

The success of any treatment for tuberculosis should be determined, not only by the early results in terms of reversal of infectiousness and roentgenographic stability, but by the ability of the patient to return to active life and to retain his health. Prior to the use of drugs and pulmonary resection, thoracoplasty had become a well-established procedure in the treatment of pulmonary tuberculosis. Since thoracoplasty is successful in a large proportion of cases, it seems appropriate to report a group so treated, with follow-up observations of sufficient length and consistency to permit comparisons with other forms of therapy.

Use of Anniversary Method of Evaluation

Late results of thoracoplasty have been reported during recent years by several writers. The number of patients studied and the duration of follow-up observation, together with the year of the report, are shown in table 1. Only one of these reports gives a year-by-year account of each patient's status, namely, the subgroup of 282 followed for five years by Hagn-Meincke (6).

In an earlier paper (2), a plea was made for the reporting of findings at five-year intervals to provide information regarding long-term results and to permit comparison of groups of patients treated by different regimens. A ten-year follow-up of the group originally studied has been completed. The findings were very similar to those at five years except that additional relapses and deaths had occurred. The writers realized that consideration of the status year by year would be of greater value, and a graph showing these data was prepared. Using a method of evaluation suggested by Bosworth (10), a broader study was then made which included additional patients with three to nine years of observation. As this graph coincided closely with that of the ten-year group, it was decided that the present report should include the data on the larger group, with emphasis on the year-by-year description of status.

Such reporting of results will be of assistance in comparing several methods of treatment, for example, thoracoplasty and the more recent excisional surgery.

PLAN OF INVESTIGATION

Analysis of findings: The findings in a group of 238 patients, 146 from the Hermann M. Biggs Memorial Hospital and 92 from the Mount Morris Tuberculosis Hospital, have been analyzed. The patients underwent thoracoplasty during the calendar years 1937–1947 and were followed through 1950. (Four patients operated upon elsewhere and admitted for surgical revision were excluded.) All of the present group were treated during the pre-streptomycin,

[1] From Hermann M. Biggs Memorial Hospital, Ithaca, New York.

TABLE 1

PREVIOUSLY PUBLISHED FOLLOW-UP STUDIES OF PATIENTS WHO HAD THORACOPLASTIES, CLASSIFIED BY AUTHOR AND YEAR PUBLISHED

AUTHOR AND YEAR PUBLISHED		PATIENTS STUDIED	PERIOD FOLLOWED
			years
Skinner *et al.* (1)	1941	100	5–15
Douglass (2)	1947	102	5
Rubin *et al.* (3)	1949	168	2–6
Kinsella *et al.* (4)	1949	613	5–26
Gutheil *et al.* (5)	1950	254	2–10
Hagn-Meincke (6)	1950	420	3–7
		282	5
Lees *et al.* (7)	1951	278	5–15
Adie *et al.* (8)	1952	334	1–17

pre-resection era, and it is believed that the results indicate what may be accomplished by thoracoplasty in association with bed-rest treatment.

The basis of case selection was not materially changed during the ten-year period. The surgical techniques remained generally the same, but both their application and the postoperative care improved as experience accumulated.

Follow-up information: For approximately 85 per cent of the patients, the follow-up information has been obtained from the hospital files, from other tuberculosis hospitals, and from health departments. For the others, information was obtained by personal contact and by correspondence with physicians and patients.

For the purpose of the study, the results of treatment have been classified as follows:

The criteria for the "arrested" group complied with the 1950 National Tuberculosis Association *Diagnostic Standards:* The chest roentgenogram showed no evidence of cavity; sputum was absent or, if present, was negative for acid-fast bacilli on microscopic examination, an occasional positive among many negatives being disregarded. Patients were, however, continued in this group following discharge only if able to carry out reasonable physical activity.

The "active" group included all patients who consistently had sputum positive for acid-fast bacilli on microscopy, regardless of the reduction of bacillary content or sputum volume. It also included all those who had persistent chest-wall sinuses and one who was a respiratory cripple.

Deaths from tuberculosis comprised one group (died-TB), and were separated from the nontuberculous deaths (died-NTB) and losses to follow-up study (lost).

OBSERVATIONS

Patients with Parenchymal Disease

The major interest in this presentation lies in the group of 205 patients with active parenchymal disease. The age and sex distribution at the time of operation is shown in table 2. The character of disease is indicated somewhat arbitrarily by grouping the patients according to cavity size, as in table 3. All patients

had sputum positive for acid-fast bacilli at or near the time of the operation, with the exception of 4 whose sputum had been negative for more than six months. The duration of disease prior to operation was more than two years in 68 per cent.

On review of the records, it is impressive that these patients, particularly in the earlier years, had had prolonged treatment which was unsuccessful in achieving arrest of disease. In later years, thoracoplasty was used increasingly as the primary method of collapse, and the duration of known disease prior to surgery was shorter.

Forty-three of the 205 patients studied (21 per cent) had no demonstrable contralateral disease; 127 patients (62 per cent) had contralateral disease which was regarded as stable; 21 patients were under treatment by contralateral pneumothorax at the time of operation, and 14 had active contralateral disease.

In table 4, follow-up data on the 205 patients are presented. The patient's condition is assessed at a point twelve months following operation and at yearly intervals thereafter. Figure 1 shows graphically the values of columns (12)–(17) in table 4, i.e., the percentage of patients in each category to be expected at each anniversary under the assumption that the experience of those with in-

TABLE 2

MALE AND FEMALE PATIENTS WITH PARENCHYMAL DISEASE, CLASSIFIED BY AGE AT TIME OF OPERATION

AGE AT TIME OF OPERATION	PATIENTS WITH PARENCHYMAL DISEASE		
	Both Sexes	Male	Female
All ages	205	87	118
Less than 20 years	11	4	7
20 to 29 years	68	33	35
30 to 39 years	80	29	51
40 to 49 years	39	17	22
50 years and older	7	4	3

TABLE 3

MALE AND FEMALE PATIENTS WITH PARENCHYMAL DISEASE, CLASSIFIED BY SIZE OF CAVITY

SIZE OF CAVITY	PATIENTS WITH PARENCHYMAL DISEASE		
	Both Sexes	Male	Female
Total	205	87	118
No cavity	26	7	19*
0.5–1.9 cm.	55	29	26
2.0–3.9 cm.	64	28	36
4 cm. and larger	60	23	37

* Twelve of these had endobronchial disease.

complete follow-up will parallel that of the patients actually observed. The deaths and losses are accumulated from year to year. All patients who achieved arrest and later experienced relapse are reassigned to the active category and are shown in the cross-hatched area of figure 1.

In commenting on figure 1, it was found that sputum conversion occurred early and that the proportion of patients with "arrested" disease remained almost constant after the second year. The "conversion" to negative on microscopy postoperatively occurred as follows: less than three months, 45 per cent; three to six months, 15 per cent; six to twelve months, 21 per cent; more than twelve months, 19 per cent.

Data regarding "conversion" by culture are lacking in 25 per cent because of the limited and inconsistent use of cultures of sputum or gastric contents, particularly in the earlier years of this study. Among the remainder, "conversion" by microscopy was followed closely by cultures negative for *M. tuberculosis* in 70 per cent while, in an additional 20 per cent, "conversion" by culture was delayed. Ten per cent of those patients with tuberculosis classified as "arrested" continued to have occasional cultures positive for tubercle bacilli.

A review of the factors relating to the outcome in this group of patients indicates that cavity size and the age of the patient at operation were not statistically significant. The percentage of those whose disease became arrested was greater among females than males, with 75 per cent with arrested disease among the former, compared with 64 per cent among the latter. The chief difference occurred in the age groups of thirty and older.

Relapses, which total 15, occurred at varying intervals during the time of study, with the greatest number in the fourth postoperative year.

Relapse rates: Figure 2 shows the annual relapse rate for each year after thoracoplasty. Half of the relapses occurred because of reactivation of disease in the contralateral lung. Re-treatment took the form of contralateral thoracoplasty in 2 and was successful in one; revision of thoracoplasty in 2; and bed rest in 11, with one patient achieving arrest of the disease. Two of the 15 patients died, 2 were returned to the "arrested" status and, in 11, the tuberculosis remained active. Preliminary data, not presented, suggest that re-treatment by chemotherapy and excision will significantly improve the results achieved by older methods.

Death rates: Thirty-seven deaths occurred during the ten-year period. Figure 3 shows the annual death rates of the 32 patients who died with active tuberculosis; of these, 6 died during the first sixty days following thoracoplasty (2 of contralateral spontaneous pneumothorax). Three deaths among the patients with arrested parenchymal disease were due to cor pulmonale. Two other deaths followed secondary operations.

A significant factor relating to the tuberculosis deaths is the extent of the thoracoplasty. Among the patients who had resection of six ribs or less, whose thoracoplasty was completed, there were 4 deaths due to progressive tuberculosis and one death due to contralateral spontaneous pneumothorax. This mortality is lower than that which occurred among those whose thoracoplasty

TABLE 4

PATIENTS TREATED BY THORACOPLASTY 1938–1947, CLASSIFIED BY STATUS AT EACH ANNIVERSARY

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	(12)	(13)	(14)	(15)	(16)	(17)
ANNIVERSARY	LIVING AT ANNIVERSARY			SINCE PREVIOUS ANNIVERSARY			TOTAL	INCOMPLETE	FACTORS		EXPECTED PERCENTAGES					
	Arrested	Active		Died		Lost			Provisional	Correction	Arrested	Active		Died		Lost
		Unremitting	Due to Relapse	Tuberculosis	Nontuberculous Disease							Unremitting	Due to Relapse	Tuberculosis	Nontuberculous Disease	
0	5	200	—	—	—	—	205	—	1.0	0.4878	2.44	97.56	—	—	—	—
1	100	96	—	9	—	—	205	—	1.0	0.4878	48.78	46.83	—	4.39	—	—
														4.39		
2	140	51	—	4	—	1	196	—	1.0	0.4878	68.29	24.88	—	1.95	—	0.49
														6.34		*0.49*
3	150	35	1	4	1	—	191	—	1.0	0.4878	73.17	17.07	0.49	1.95	0.49	—
														8.29	*0.49*	*0.49*
4	125	24	6	3	1	2	161	25	1.1553	0.5636	70.45	15.22	1.69	1.69	0.56	1.13
														9.98	*1.05*	*1.62*
5	121	19	6	2	1	—	149	6	1.0403	0.5863	70.94	11.14	3.52	1.17	0.59	—
														11.15	*1.64*	*1.62*
6	117	13	7	3	1	1	142	4	1.0282	0.6028	70.53	7.84	4.22	1.81	0.60	0.60
														12.96	*2.24*	*2.22*
7	110	11	5	1	—	—	127	10	1.0787	0.6502	71.52	7.15	3.25	0.65	—	—
														13.61	*2.24*	*2.22*
8	93	5	7	4	1	—	110	16	1.1455	0.7448	69.27	3.72	5.21	2.98	0.74	—
														16.59	*2.98*	*2.22*
9	69	3	5	2	—	—	79	26	1.3291	0.9899	68.30	2.97	4.95	1.98	—	—
														18.57	*2.98*	*2.22*
10	53	1	4	—	—	—	58	19	1.3276	1.3142	69.65	1.31	5.26	—	—	—
														18.57	*2.98*	*2.22*

(1) Number of years after operation.
(2) Number of living patients with arrested disease at anniversary of operation.

(3) Number of patients living at anniversary with unremittingly active disease.
(4) Number of patients living at anniversary with disease active due to relapse.
(5) Number who died of tuberculosis since previous anniversary.
(6) Number who died of causes other than tuberculosis since previous anniversary.
(7) Number lost since previous anniversary.
(8) Total number at anniversary, sum of columns (2) to (7) inclusive.
(9) Number of "incomplete" patients at anniversary. These patients were alive and traced at the previous anniversary but had too short a follow-up to attain the specified anniversary.
(10) Provisional factor for anniversary $= \frac{\text{column (8)} + \text{column (9)}}{\text{column (8)}}$.
(11) Correction factor for anniversary = column (10) × correction factor for previous anniversary. The correction factor for anniversary $0 = \frac{100}{205}$.
(12) Expected percentage of living patients with arrested disease at anniversary: column (2) × column (11).
(13) Expected percentage of patients with unremittingly active disease at anniversary: column (3) × column (11).
(14) Expected percentage of patients with disease active due to relapse at anniversary: column (4) × column (11).
(15) Expected percentage of patients dead of tuberculosis at anniversary: column (5) × column (11). Cumulative percentages in italics.
(16) Expected percentage of patients dead of causes other than tuberculosis at anniversary: column (6) × column (11). Cumulative percentages in italics.
(17) Expected percentage of patients lost at anniversary: column (7) × column (11). Cumulative percentages in italics.

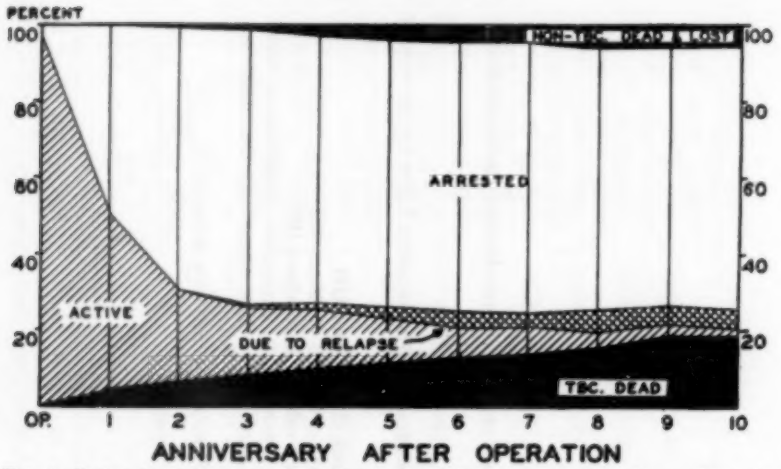

FIG. 1. Status at anniversary. Two hundred and five patients with thoracoplasty for parenchymal disease.

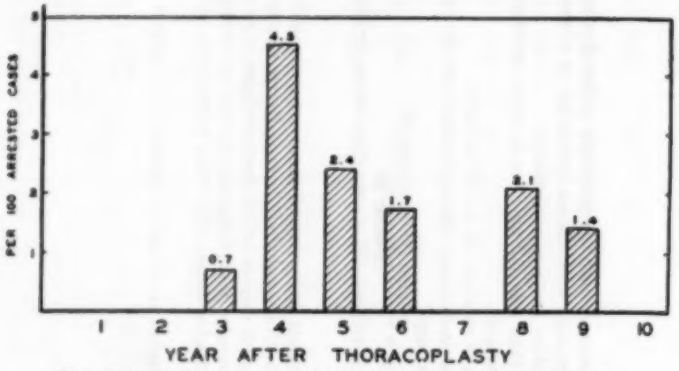

FIG. 2. Annual relapse rate for each year after thoracoplasty.

required the resection of seven or more ribs and may reflect the limited extent and relatively favorable location of the original disease.

In the total series, one-eighth of the deaths from all causes were due to cor pulmonale. Spain and Handler (9) have suggested that right heart strain results from thoracoplasty of long standing, possibly on a mechanical basis. In addition, the role of parenchymal changes in the remaining functioning lung will require evaluation.

Patients with Pleural Problems

An additional small group of 33 patients who presented problems related to the pleura had sputum negative for acid-fast bacilli at the time of surgery. The

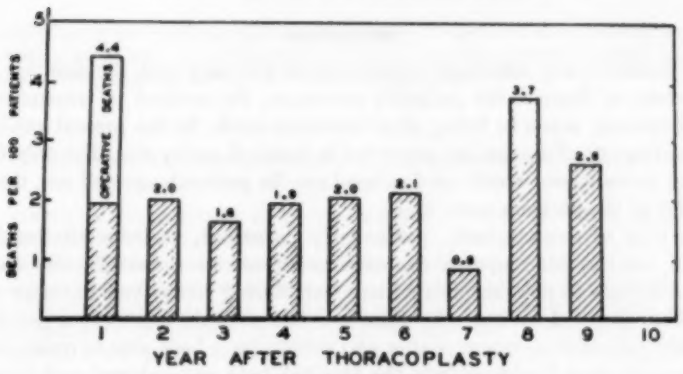

FIG. 3. Tuberculosis death rates.

TABLE 5

PATIENTS WITH PLEURAL PROBLEMS IN SPECIFIED STAGE, CLASSIFIED BY REASONS FOR THORACOPLASTY

REASON FOR THORACOPLASTY	PATIENTS WITH PLEURAL PROBLEMS IN SPECIFIED STAGE			
	All Stages	Minimal	Moderately Advanced	Far Advanced
All reasons	33	1	17	15
Inexpansile lung	12	—	8	4
Empyema, tuberculous	15	—	7	8
Empyema, nontuberculous	3	—	2	1
Empyema, mixed	3	1	—	2

Twenty-three had 10 ribs or more resected.
Ten had 9 ribs or less resected.

reasons for operation in each instance are presented in table 5. All patients had had sputum positive for acid-fast bacilli at some time, and all had been treated by pneumothorax. Better understanding of the limitations of pneumothorax is reflected in the fact that the majority of these patients were operated upon during the first five years of the study. The surgical procedures ranged from limited paravertebral to extensive Schede thoracoplasties. The initial lesions were far advanced in 15, moderately advanced in 17, and minimal in one. It is important to recognize that there must have been necrotic tuberculous lesions in the underlying lung tissue in all of the patients at the time of thoracoplasty.

Relapse of parenchymal tuberculosis occurred in only one patient and was on the contralateral side. A second patient had an exacerbation of tuberculous empyema and had tubercle bacilli in the sputum with "conversion" of sputum and recovery from empyema following surgery. In this group of 33 patients, 2 deaths occurred from cor pulmonale at the eighth and ninth postoperative years, respectively. There were no deaths from progressive pulmonary tuberculosis.

DISCUSSION

The results of any treatment in tuberculosis will vary with the duration, type, and extent of disease; the patient's resistance; the method of treatment; and the adjustment made to living after return to work. In the present study, the type and extent of disease are presented in terms of cavity size. The only factors relating to resistance which are discussed are the patient's age and sex; the great majority of the patients were white.

The type of thoracoplasty, particularly its extent, varied with the disease pattern, but the subgroups are too small and numerous for satisfactory analysis. With reference to post-hospital adjustment, during recent years greater efforts have been directed toward rehabilitation. The patients represent a group with generally favorable economic status who usually have been able to make suitable adjustments after discharge from the hospital, both occupational and in respect to care of their health.

SUMMARY

The results of thoracoplasty have been evaluated on the basis of status on the anniversary of operation.

Two hundred and five patients were operated upon for parenchymal disease.

The study shows 70 per cent of the patients with disease arrested at the end of ten years.

Arrest of the disease occurred for the most part by the second anniversary and the incidence of arrests showed little change thereafter.

Relapses occurred throughout the ten-year period. In the absence of resection, the outlook was poor.

Deaths occurred at an almost uniform rate after the initial postoperative period, during which one-sixth of the deaths occurred. Approximately one-tenth of the later deaths were due to cor pulmonale.

Thirty-three patients were operated upon for pleural disease. There were no deaths due to tuberculosis, and one patient had exacerbation of contralateral parenchymal disease. Two patients in this group died of cor pulmonale.

SUMARIO

La Historia Subsecuente de la Tuberculosis Pulmonar. II. Toracoplastia, Diez Años de Observación

Los resultados de la toracoplastia fueron justipreciados a base del estado del enfermo al cumplirse el décimo aniversario de la operación.

Doscientos cinco enfermos fueron operados por afección parenquimatosa.

El estudio revela que en 70 por ciento de los enfermos la dolencia estaba estacionada al cabo de diez años.

El estacionamiento tuvo lugar en la mayor parte para el segundo aniversario, revelando poca modificación después.

Hubo recidivas durante todo el período de diez años. Cuando no se aplicó la resección, el pronóstico fué malo.

Sobrevinieron muertes en proporción casi uniforme a partir del período postoperatorio inicial, durante el cual ocurrió la sexta parte de los fallecimientos. Aproximadamente la décima parte de las muertes más tardías se debieron a corazón pulmonar.

A 33 enfermos se les operó por problemas pleurales. No hubo en ellos muertes debidas a tuberculosis y un enfermo experimentó exacerbación de una enfermedad parenquimatosa contralateral. Dos pacientes fallecieron de corazón pulmonar.

RESUME

Histoire des suites de la tuberculose pulmonaire: II. Thoracoplastie; Dix années d'observation du malade

Une évaluation des résultats de la thoracoplasie, fondée sur l'état du sujet, a été effectuée à l'anniversaire de l'opération.

Deux cent-cinque malades furent opérés pour lésions du parenchyme.

L'étude montre 70 pour cent de cas stabilisés à la fin d'une période de dix années.

La stabilisation était aquise chez la plupart d'entre eux à la date du deuxième anniversaire, sans que des modifications importantes soient observées ultérieurement.

Des rechutes se sont produites au cours de la période de dix années. En l'absence de résection le pronostic était mauvais.

Après la période post-opératoire initiale, au cours de laquelle un sixième des décès se sont produits, la proportion des décès a été presque uniforme. Approximativement un dixième des décès tardifs sont imputables au coeur pulmonaire.

Trente -trois malades furent opérés pour lésions pleurales. Il ne s'est produit aucun décès imputable à la tuberculose. Un des malades a présenté une aggravation de la lésion du parenchyme du poumon opposé. Deux malades ont succombé, la mort était due au coeur pulmonaire.

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THE ROUTINE ADMISSION CHEST ROENTGENOGRAPHIC PROGRAM AT THE LOS ANGELES COUNTY HOSPITAL[1,2,3]

A Report of the First Year

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(Received for publication July 13, 1953)

INTRODUCTION

The development of extensive and relatively economical tuberculosis case-finding programs has been one of the primary objectives of those concerned with the control of this disease. The value of the routine roentgenographic examination of the chests of all patients admitted to general hospitals has been recognized for almost thirty years, and its advantages over other case-finding methods have been pointed out repeatedly. Yet, until quite recently the major emphasis has been on the mass chest roentgenographic survey, such as those conducted in various cities throughout the country by the Public Health Service in conjunction with the local health organizations. In order for this method to be effective in decreasing the prevalence of tuberculosis, each city would have to be re-surveyed periodically. This has proved to be impracticable for many reasons. One of the greatest benefits of the mass survey has been to demonstrate to both the medical profession and the public the existing high prevalence of tuberculosis and the need for a continuous, efficient, case-finding program in each community.

Many cities maintain mobile photofluorographic units which conduct a continuous survey of the population and concentrate on those economic and geographic areas in which the greatest prevalence of tuberculosis is to be expected. However, the number of people who voluntarily present themselves for examination at these units decreases rapidly following an active mass survey. Consequently the cost per examination rises while the yield in disease discovered falls sharply. Also it is quite difficult to get older persons to visit these mobile units; yet it is the older age groups which have the highest prevalence of tuberculosis as well as other pulmonary and cardiovascular diseases.

Review of Literature

Numerous studies have been published concerning the prevalence of tuberculosis in patients admitted to general hospitals. As reviewed by Bryant (1) in 1950, these reports showed that there was roentgenographic evidence of reinfection tuberculosis

[1] From the departments of radiology of the School of Medicine, University of Southern California, and of the College of Medical Evangelists, and of the Los Angeles County Hospital.

[2] Supported by a grant from the Los Angeles County Tuberculosis and Health Association.

[3] Presented before the General Closing Session at the annual meeting of the National Tuberculosis Association, Los Angeles, California, May 22, 1953.

in 2.6 to 8.1 per cent of these patients and that the rate of active tuberculosis varied from 0.6 to 1.8 per cent. The results of the admission chest roentgenographic program at the University of Michigan from 1941 to 1949 were reported by Hodges (2), who found 3.2 per cent of significant tuberculosis with 1.28 per cent of active cases. The first two years, 1947 to 1949, of the admission program conducted in a large number of hospitals in New York State showed a prevalence of 1.13 per cent, with 0.25 per cent of proved active cases of tuberculosis (3). Schneider and Robbins (4) reviewed the admission chest roentgenographic program of the Veterans Administration. Approximately one-half million veterans were examined in 99 general and 34 neuropsychiatric hospitals. They found evidence of tuberculosis in 2.42 per cent of the patients. Active tuberculosis was present in 0.8 per cent.

On the other hand, the prevalence of tuberculosis in the general population, as shown by mass chest surveys, is considerably less than that found in hospital admissions. The results of 17 community-wide surveys, as summarized by the Public Health Service (5), showed the prevalence of tuberculosis throughout the United States to vary from 0.6 to 2.8 per cent, with an average of 0.9 per cent. Following clinical evaluation, it was found that 0.1 per cent were active cases and 0.6 per cent were inactive cases of tuberculosis (0.2 per cent were lost to follow-up). Seventy-five per cent were previously unrecognized.

From this comparison, it would appear that a widespread hospital admission chest program should be the greatest and most economical means for finding tuberculosis, considering that approximately 16,000,000 people are admitted each year to general hospitals throughout the United States. These patients constitute a large segment of the population readily available for examination, rapid diagnosis, and follow-up.

A large proportion of those admitted to general hospitals are in the older age groups, in which it has been shown that the highest prevalence of tuberculosis exists. Medlar (6), in a study of necropsy material from private and public general hospitals, found that the prevalence of clinically unrecognized, pathologically significant tuberculosis was approximately 10 per cent for both types of institutions. He found an equal occurrence in males and females up to the age of thirty, but that after fifty years there was considerably more tuberculosis in males than in females. Most of the significant unsuspected tuberculosis occurred after the age of fifty years.

In addition, a roentgenogram of the chest obtained on admission contributes greatly to the care of the patient. It permits early demonstration of nontuberculous pulmonary and cardiovascular disease and is of greater value than most other routine laboratory procedures.

It has been shown repeatedly that medical and nursing students who were nonreactors to tuberculin became positive reactors soon after they came in contact with the patients on general medical wards. Unsuspected tuberculosis in the hospitalized patient is a frequent source of infection for medical, nursing, and other hospital personnel. The early detection and isolation of these patients is of the greatest importance.

Notwithstanding the above advantages and the fact that the American Medical Association, Public Health Service, National Tuberculosis Association, and other organizations have recommended routine admission roentgenograms of the chest for many years, most hospitals do not provide this service. In 1948, only 247 of 4,539 general hospitals had such programs (7). While many more are now in operation, the number is not accurately known (8). Only a few have been undertaken in

hospitals of more than 500-bed capacity. There are many reasons why more hospitals, particularly the larger ones, have not initiated admission chest programs. There are primarily financial (new equipment and additional personnel) and administrative in nature. Ochsner's experience in a 700-bed hospital led him to state that the administrative problems were almost insurmountable (9).

The purpose of the present report is to describe the administration, operating procedures, and results of the first year of the routine admission chest roentgenographic program at the Los Angeles County Hospital, which has a capacity of 3,413 beds and had 74,663 inpatient admissions during 1951–1952. The only other public general hospital of similar size and type known to the writers which has a photofluorographic unit is the Charity Hospital of New Orleans. Although the New Orleans group reports making approximately 50,000 examinations per year, their program is designed primarily for outpatients (10).

ADMINISTRATION AND PROCEDURE

The admission chest roentgenographic program of the Los Angeles County Hospital was begun in October, 1951. The Department of Radiology has been responsible for the interpretation of the photofluorograms, the administration of the program, and its integration into the hospital routine. The examinations have been conducted continuously, twenty-four hours per day and seven days per week. Although the basic procedure has been similar to that employed elsewhere, the administrative problems encountered have been proportionately more numerous and complicated than in smaller institutions. Regardless of the enthusiasm of the radiologist or other persons, it is essential to realize that an admission chest roentgenographic program requires the active cooperation of every department in the hospital.

Equipment: It is generally accepted that photofluorography, preferably using 70 mm. roll film, is the most satisfactory method of examination in larger institutions. Because a large proportion of those admitted to the Los Angeles County Hospital are stretcher patients, it was necessary to have equipment designed and constructed to permit the examination of patients in the recumbent position as well as in the standing or the sitting positions (figure 1). This was accomplished by having two photofluorographic units operated from a single control panel, the proper unit being selected by means of a toggle switch. One is a conventional unit used to examine ambulatory or sitting patients. The other, for the examination of patients in the supine position, consists of a standard photofluorographic hood and camera suspended vertically from a tubestand. The tube, which is under the table, has been recessed into the floor to maintain a 40-inch target-film distance. In this manner the exposures are made in the posterior-anterior projection, and the resulting roentgenograms are quite comparable in appearance to those obtained in the upright position (figure 2). This equipment was installed adjacent to the admitting room in order to incorporate the examination most efficiently into the hospital admission procedure.

During the period which this report covers, the patients examined in the recumbent position were moved from stretchers to a radiographic table which had been placed on tracks for ease of positioning. It was soon discovered that many of the seriously ill or injured patients could not be examined because it was hazardous to transfer them from their stretchers to the table and back again. Also, this was found to be a time- and energy-consuming procedure. As a result, a special stretcher was designed which could be used for general hospital purposes and also would serve as a "radiographic table" (figure 1). Since this stretcher has

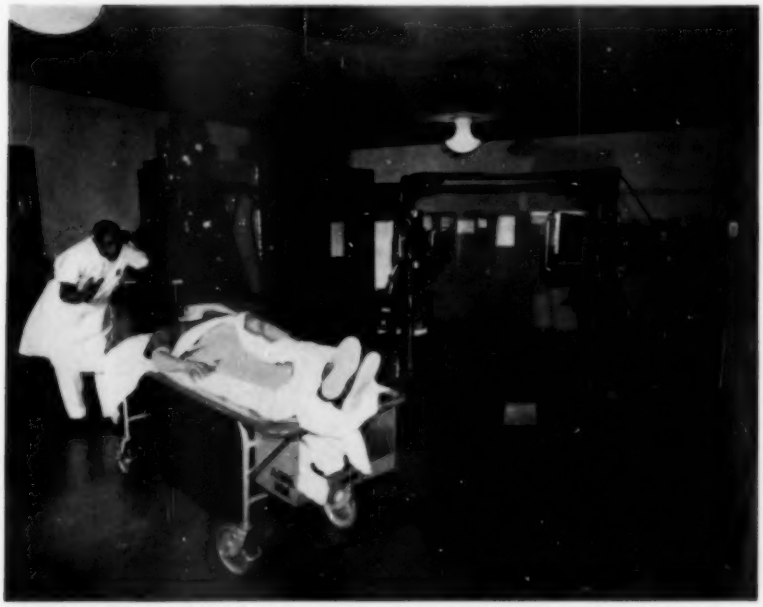

FIG. 1. Seventy-millimeter photofluorographic unit for examination of standing or sitting patients (right) and recumbent patients (left). Both cameras operated by single control stand located behind protective lead screen. Special stretcher used as radiographic table and also for general hospital purposes.

been in use, it has been possible to examine all patients except a few in critical condition. This has proved to be a very important feature in the success of the program.

At present, the patient is taken from the ambulance and placed directly on the special stretcher, on which he remains until he reaches his assigned ward. The stretcher-pad on which the patient lies does not appreciably affect the diagnostic quality of the minifilm.

Examination of patients: After examining the patient, the admitting-room physician checks the following form which has been stamped on the face sheet of the admitting record:

____1. Take minifilm
____Standing
____Sitting
____Lying Down
____2. Do not take minifilm

Since the special stretchers have been acquired the last category is reserved for critically ill patients.

From the admitting room the patient is routed to the photofluorographic unit. No attempt is made to undress the patient except for readily removable metallic objects. The technician fills out a two-part "Admission Chest X-ray Report" (figure 3), entering on it the following information: permanent hospital file number, date of examination, name, age, sex, and race. There are two sets of serially numbered report forms. Those beginning with the number 1 are assigned to the conventional photofluorographic unit, and those beginning with the number 2 are assigned to the unit for the examination of recumbent patients.

Following the examination of the patient, the face sheet of the hospital record is stamped "minifilm taken" and the number of the minifilm is entered thereon.

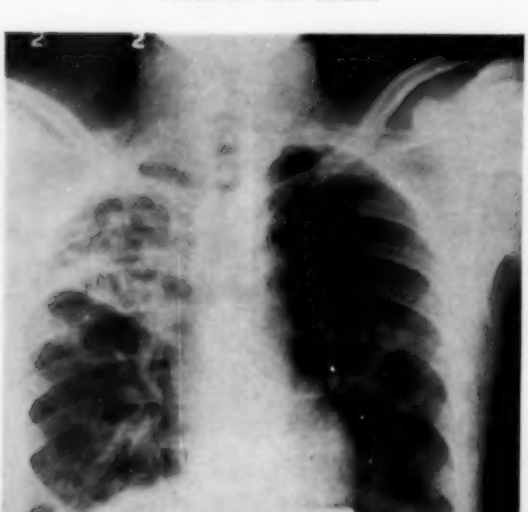

FIG. 2. Seventy-millimeter photofluorogram, demonstrating far advanced tuberculosis taken with the patient in the supine position. The minifilm, made in the posterior-anterior projection, is comparable in appearance to one obtained in the upright position.

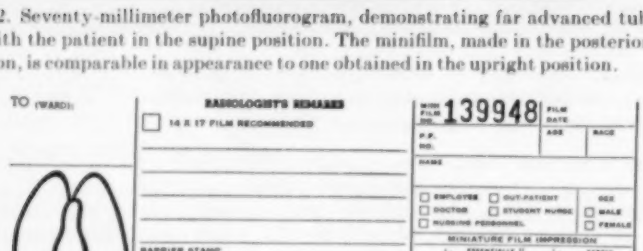

FIG. 3. Minifilm report form.

The films are processed at midnight so that they may be dry and ready for interpretation in the morning.

Most hospitals include only adults in their admission chest roentgenographic program because of the low prevalence of tuberculosis in those less than sixteen years of age. However, all age groups, even infants, are being examined at the Los Angeles County Hospital. The yield of significant nontuberculous pulmonary and cardiac disease has been sufficiently great to warrant its use as a screening device in the younger age groups.

The roentgenograms obtained in infants and children have been of surprisingly good quality (figure 4). Difficulty is sometimes encountered in positioning these patients. *It should be emphasized that, to avoid the hazard of radiation exposure to personnel, infants are not to be held in position by the technicians but are to be held by their parents.* Respiratory movement

FIG. 4. Seventy-millimeter photofluorogram of a five-month-old infant, demonstrating the generally satisfactory quality of the roentgenograms obtained in infants and children.

in these young patients has not been a problem as the photo-timed exposures are in the range of one-twentieth to one-thirtieth of a second. The amount of radiation received by an infant is not considered to be harmful. The radiation to the near skin surface (skin dose) has been measured and found to average 0.15 r per exposure.

Outpatients are not included in the admission chest program. There are many patients who are classified by the hospital as temporary or interim admissions. These are patients who are sent to admitting wards for treatment and to determine the necessity for actual hospital admission. Most of them do not remain in the hospital for more than a few hours. Nevertheless, these patients are included in the program.

Patients are photofluorographed each time they are admitted to the hospital. This is done to avoid unnecessary delays in the admitting room caused by waiting for the patient's record of previous admissions to arrive from the chart room. While some patients had repeated minifilm examinations during the year, this has not been a significant problem since the yearly readmission rate is approximately 1.25 for inpatients and 3.0 for interim admissions.

Due to insufficient hospital personnel, no attempt is made to examine those patients who were not photofluorographed on admission. However, when possible, they are sent to the photofluorographic unit before being discharged. This group of patients has decreased from approximately 40 per cent to 20 per cent of those available for examination since the special stretchers have been acquired.

Examination of personnel: Interns, resident physicians, student nurses, and personnel attached to the Tuberculosis Unit of the hospital have a minifilm examination every six months. The remainder of the hospital personnel is examined yearly. The results of these examinations are not included in this report as this procedure was begun some time after the admission chest program and the number examined is insufficient for analysis at the present time.

Clerical procedures: The processed film and minifilm report forms are delivered to the

Department of Radiology at 8:00 a.m. The number of the ward to which the patient is sent is obtained from the hospital admission records and entered on the minifilm reports.

The minifilm report is a duplicate form. The original is delivered to the ward and attached to the patient's chart by one of the clerks of the department. The carbon copy is filed in the X-ray Department.

The requisitions for the 14- by 17-inch film examinations recommended by the radiologist are filled out, and the minifilm impression and area of involvement are entered on the requisition. The files of the X-ray Department are checked to determine whether the patient has had a recent roentgenographic examination of the chest and, if so, whether a repeat study is indicated. These requisitions are delivered to the ward with the corresponding minifilm reports. This procedure is completed by 2:00 p.m. of the day following the patient's admission to the hospital. The requisitions for 14- by 17-inch film examinations are then signed by the ward intern or resident, who adds the appropriate clinical information. These requisitions are retained on the ward file until the patient is sent for by the X-ray Department.

The examinations requested by the radiologist are completed within forty-eight hours, except for those instances in which the patient is too ill to be brought to the Department, has died, or, in the case of the interim or temporary admissions, has been discharged from the hospital.

A medical record librarian checks the charts of the patients who have been discharged to determine whether follow-up for tuberculosis is required. A form to be used for statistical analysis is made out for each one who has had a minifilm examination.

Minifilm interpretation: Most of the minifilms are interpreted by experienced radiologists. The resident physicians in radiology participate in the interpretation as part of their training. A shortage of personnel has not permitted double "reading" of the minifilm, although the value of this practice has been well established.

The admission chest roentgenographic report form is similar to those in general use but has been modified to meet particular needs (figure 3).

Miniature film impressions:

Essentially negative. Includes all normal chests and those in which there are minor abnormalities considered to be of no clinical significance: anomalies and old fractures of the ribs, arteriosclerosis of the aorta in the aged, et cetera.

Unsatisfactory film. Includes films which are unsatisfactory because of faulty exposure, positioning, movement, et cetera.

Calcification only. In most instances in which a solitary calcification or a few pulmonary or mediastinal calcifications are present, the chest is classified as essentially negative. This category is reserved for those cases in which the calcification may be of clinical significance.

Probable tuberculosis, urgent. In these cases the findings are strongly suggestive of active tuberculosis. The area of involvement is indicated under the column "Radiologist's Remarks," and a 14- by 17-inch film examination is automatically recommended. Both the minifilm report and the 14- by 17-inch film requisition are stamped "Barrier" in large red letters. As soon as the report reaches the ward, the patient is placed in isolation until the diagnosis is disproved or the patient is transferred to the tuberculosis service.

Suspected tuberculosis. This classification includes all lesions which may possibly be either active or inactive tuberculosis. The area of involvement is indicated under "Radiologist's Remarks," and a 14- by 17-inch film examination is automatically recommended. It has been the policy to "over-read" the minifilms deliberately so that a large number of patients with questionable pulmonary lesions are included in this category. These patients are not isolated.

Probable nontuberculous pulmonary chest disease. All significant pulmonary lesions in which tuberculosis is not suspected are included in this group. When a diagnosis such as lobar pneumonia, pleural effusion, et cetera, can reasonably be as-

sumed, the suspected diagnosis is indicated under "Radiologist's Remarks" and the area of involvement is sketched on the chest outline included on the minifilm report form. In these cases, no 14- by 17-inch film is recommended. Whenever there is any question as to the diagnosis, a 14- by 17-inch film is requested. The ward physician may ask for a conventional roentgenographic examination of the chest whenever the minifilm report does not agree with the clinical findings, or as otherwise indicated.

Cardiovascular. All cardiovascular abnormalities are reported. A 14- by 17-inch film is requested only in unusual cases.

Other abnormalities. These include bony abnormalities, such as recent fractures or metastases, lesions of the diaphragm, et cetera. When indicated, a 14- by 17-inch film is recommended.

Mediastinum. These include mediastinal or hilar abnormalities, mediastinal masses, et cetera. A 14- by 17-inch film is requested in most instances.

Follow-up observations: All patients who are discharged from the hospital with a diagnosis of tuberculosis are reported to the appropriate health department. Inasmuch as the admission chest roentgenographic program includes temporary admissions and patients who remain in the hospital for a very short period of time, many tuberculosis suspects —and frequently some with obvious tuberculosis—are discharged before the minifilm report can be delivered to the ward or a 14- by 17-inch film can be obtained. These patients are also reported to, and followed by, either the city or county health departments.

RESULTS

From November 1, 1951, through October 31, 1952, 74,663 patients were admitted to the Los Angeles County Hospital (table 1). Of these, 63,045 patients

TABLE 1

RESULTS OF ROUTINE CHEST ROENTGENOGRAMS ON 77,789 PATIENTS ADMITTED TO LOS ANGELES COUNTY HOSPITAL FROM NOVEMBER 1, 1951, THROUGH OCTOBER 21, 1952

Bed capacity Los Angeles County Hospital			3,413		
Patients admitted to all units of hospital			74,663		
Patients admitted to Acute Unit				63,045	
Interim (temporary) admissions				14,744	
Total patients available for examination				77,789	
Individual patients available for examination			55,351*		
Patients examined before acquiring special stretchers				49,478	63.6%
Supine	27,471	57.5%			
Upright	22,007	42.5%			
Unsatisfactory examinations				1,641	2.1%
Supine	1,206	73.1%			
Upright	435	26.9%			
Satisfactory examinations				47,837	61.5%
Satisfactory examinations, individual patients			34,040*		
Patients examined after acquiring special stretchers—December 1952					81.5%
Minifilms positive					26.0%
14- by 17-inch films recommended				5,063	10.6%
Inpatient chest examinations before program, November 1, 1950–October 31, 1951				18,357	
Inpatient chest examinations during program, November 1, 1951–October 31, 1952				13,789	75.1%

* Based on yearly readmission rate of 1.25 for inpatients and 3.0 for interim admissions.

were admitted to the Acute Unit. The remainder were admitted directly either to the Contagious, Tuberculosis, or Psychiatric units and were not included in the program. In addition there were 14,744 interim admissions. A total of 77,789 patients was available for examination, of whom 49,478 (63.6 per cent) had 70 mm. photofluorograms on admission to the hospital.

More than half of the patients (57.5 per cent) were examined in the supine position, emphasizing the need for radiographic equipment designed for examining patients who can neither sit nor stand. Without such equipment, an admission chest roentgenographic program in a large general hospital cannot be successful.

The number of unsatisfactory examinations (2.1 per cent) was higher than usually reported. This may be accounted for, in part, by the fact that in the first few months of the program there was a shortage of trained personnel. Approximately 75 per cent of the unsuccessful examinations occurred in patients radiographed in the supine position. The majority of these patients were either very old or very young. There were 47,837 satisfactory examinations (61.5 per cent), representing 34,040 persons.

The special radiographic stretchers were put into use in December, 1952. Since that time the percentage of patients examined has increased from 63.6 per cent to 81.5 per cent.

Significant positive findings were recorded in 26 per cent of the satisfactory minifilms. A 14- by 17-inch film was recommended in 10.6 per cent of the satisfactory examinations. Before the onset of the program it was feared that there would be an increase in the volume of inpatient chest examinations. However, comparison with the previous year, during which there were approximately the same number of admissions, shows a decrease of almost 25 per cent. A large portion of this decrease can be attributed to a marked reduction in the number of requests for "routine" roentgenograms of the chest.

A tabulation of the minifilm interpretations is presented in table 2. Almost 10 per cent of the minifilms of the patients less than the age of one year were positive, and there was only a slight decrease (9 per cent) in positive findings in the one- to nine-year group. The majority of these positive films were classified as nontuberculous pulmonary chest disease; in most instances, pneumonia. Further investigation disclosed that frequently extensive pneumonia demonstrated by the minifilm was unsuspected clinically. This, in addition to the tuberculosis detected, justifies the inclusion of children and infants in an admission chest roentgenographic program. The Pediatric Department has enthusiastically endorsed this policy. Adolescents had the lowest incidence of positive minifilms, 6.5 per cent. More than half of the patients (53.9 per cent) more than forty-five years of age had significant pulmonary or cardiovascular disease.

In spite of the fact that 60 per cent of the patients examined were females, 51.6 per cent of the positive findings occurred in males. This is partly due to the large number of female patients in the twenty- to forty-four-year age group admitted to the obstetrical service.

TABLE 2

ADMISSION CHEST ROENTGENOGRAMS AT A GENERAL HOSPITAL

Minifilm Interpretation

AGE	SATISFACTORY MINIFILMS	TUBERCULOSIS		NONTUBERCULOUS PULMONARY CHEST DISEASE	CARDIOVASCULAR	OTHER INCLUDING MEDIASTINUM	POSITIVE MINIFILMS	
		Probable, Urgent	Suspected				Number	Per Cent
years								
Less than one	4,503	2	29	310	24	88	444	9.8
1–9	5,968	3	67	351	59	75	541	9.0
10–19	4,261	9	47	120	56	54	276	6.5
20–44	16,671	155	397	916	633	341	2,364	14.2
45 and over	16,322	305	1,115	3,613	3,808	900	8,805	53.9
Not stated	112	1	6	17	11	6	37	—
Male	19,109 (40%)	316	960	2,972	2,120	612	6,439	34.0
Female	28,728 (60%)	159	701	2,355	2,471	852	6,028	21.0
Total number	47,837	475	1,661	5,327	4,591	1,464	12,467	26.0
Per cent		1.0	3.5	11.1	9.6	3.1	1,051 minifilms had multiple findings	

A total of 4.5 per cent of the minifilms were interpreted as either probable tuberculosis (1 per cent) or suspected tuberculosis (3.5 per cent). The importance of the program as a screening method for disease other than tuberculosis is demonstrated by the following minifilm findings: nontuberculous pulmonary chest disease, 11.1 per cent; cardiovascular abnormalities, 9.6 per cent; and other miscellaneous lesions, 3.1 per cent.

A concerted effort was made to obtain a 14- by 17-inch roentgenogram within forty-eight hours after admission on all patients in whom tuberculosis was suspected. However, in 680 patients (34.5 per cent), no 14- by 17-inch films could be obtained: 75 patients had died, 260 patients had been discharged from the hospital and, in 345 patients, the reason could not be determined (table 3). The two latter groups, totaling 605 patients, were referred either to the city or county health departments for follow-up.

A final diagnosis of tuberculosis was made in 665 of the 1,299 suspects on whom a 14- by 17-inch film was obtained. In addition, 54 cases of tuberculosis were found in patients classified as having nontuberculous pulmonary chest disease. A total of 719 cases of tuberculosis was disclosed by the survey, representing 2.1 per cent of the patients examined. The tuberculosis was active in 48.6 per cent of the patients, inactive in 28.5 per cent, and the activity was undetermined in 22.9 per cent of the patients.

The minifilms were interpreted correctly in 85.5 per cent of the cases classified as *probable tuberculosis*, and in 41.4 per cent of the cases classified as *suspected*

TABLE 3

ADMISSION CHEST ROENTGENOGRAMS AT A GENERAL HOSPITAL

Final Diagnosis Tuberculosis*—Activity

	MINIFILM CLASSIFICATION			TOTAL	
	Probable Tuberculosis, Urgent	Tuberculosis Suspected	Nontuberculous Pulmonary Chest Disease	Number	Per Cent
Total	425	1,500	—	1,979	100
14- by 17-inch film not obtained†	86	594	—	680	34.5
14- by 17-inch film obtained	339	906	54	1,299	65.5
Final Diagnosis Tuberculosis					
Tuberculosis active	205	115	29	349	48.6
Tuberculosis inactive	50	142	13	205	28.5
Tuberculosis activity undetermined	35	118	12	165	22.9
Total	290	375	54	719	100.0
Accuracy of minifilm interpretation	85.5%	41.4%		55.3%	
Computed Tuberculosis (Includes Estimated Tuberculosis in Those Referred to Health Departments)					
Tuberculosis in persons in whom 14- by 17-inch film was not obtained	74	246	—	320	
Total tuberculosis in 34,040 individuals examined	364	621	54	1,039	3.1

* Individual patients.

† Died, 75; interim admissions, 260; unknown, 345. Referred to city or county health department, 605.

tuberculosis. Using these accuracy rates, the prevalence of tuberculosis was computed in those patients who were referred to the health departments. On this basis, the total number of cases of tuberculosis in the 34,040 persons examined was 1,039, or 3.1 per cent.

The age, sex, and race distribution of the 719 patients in whom a final diagnosis of tuberculosis was made is shown in table 4. Only one case of tuberculosis was detected in a patient less than one year of age. There were 26 cases in those less than fifteen years of age. The number of cases of tuberculosis increased progressively with age, approximately half the cases occurring in white males older than forty years. The total number in males was twice that in females, and the total number in whites was four times that in non-whites.

The prevalence of tuberculosis in the different age, sex, and race groups is shown in figure 5. The highest rate of tuberculosis, 6.7 per cent, occurred in the non-white males from thirty-one to forty years of age. The highest prevalence

TABLE 4

ADMISSION CHEST ROENTGENOGRAMS AT A GENERAL HOSPITAL
Final Diagnosis Tuberculosis (Total)*—Age, Sex, and Race

AGE	WHITE†			NON-WHITE			ALL RACES		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
years									
Less than one	—	1	1	—	—	—	—	1	1
1–5	5	4	9	5	2	7	10	6	16
6–14	2	4	6	3	—	3	5	4	9
15–20	10	5	15	1	1	2	11	6	17
21–30	21	32	53	12	19	31	33	51	84
31–40	45	54	99	27	12	39	72	66	138
41–50	76	10	86	12	8	20	88	18	106
51–60	80	23	103	10	5	15	90	28	118
More than 60	167	41	208	14	8	22	181	49	230
Total.....	406	174	580	84	55	139	490	229	719

* Individual patients.
† Includes Latin Americans.

in white males was 5.5 per cent and occurred in the fifty-one- to sixty-year age group. The rate in white males was 3.6 per cent, almost the same as in non-white males (3.4 per cent). Tuberculosis was three times as frequent in white males (3.6 per cent) as in white females (1.2 per cent) and four times as frequent in non-white males (3.4 per cent) as in non-white females (0.9 per cent). There was no marked difference in prevalence between whites (2.2 per cent) and non-whites (1.6 per cent). The prevalence of tuberculosis in all groups was 2.1 per cent, with the frequency in males (3.6 per cent) three times as great as in females (1.1 per cent). The tuberculosis rate was 0.8 per cent in the age group of one to five years, and 0.6 per cent in the age group of six to fourteen years.

Almost two-thirds (63.5 per cent) of the 719 patients with tuberculosis were unaware that they had the disease (figure 6). It is particularly significant that approximately 60 per cent of the 349 cases of active tuberculosis were previously unknown (28.9 per cent of the persons with tuberculosis).

The prevalence of tuberculosis per thousand persons admitted to the Los Angeles County Hospital is indicated in table 5. In each thousand persons examined, a final diagnosis of tuberculosis was made in 21 patients. Fourteen of the cases were previously unknown. There were 10 cases of active tuberculosis, of which 6 cases were previously unknown. Including those patients referred to the health departments (computed tuberculosis), tuberculosis occurred in 31 patients, in 20 of whom it was previously unknown. Fifteen patients had active tuberculosis, in 9 of whom it was previously unknown.

The cost of the first year of the admission chest roentgenographic program is shown in table 6. The cost per minifilm examination was $0.76. A comparable cost is reported in most of the mass roentgenographic surveys. The cost of diagnosing a case of previously unknown active tuberculosis was $180. This

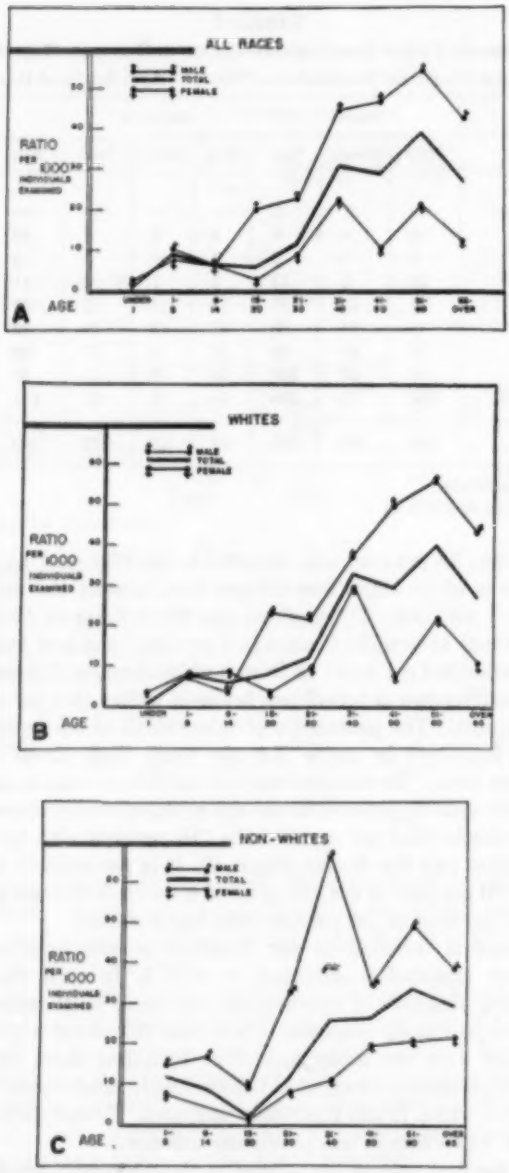

FIG. 5. Final diagnosis tuberculosis (total) prevalence per 1,000 individual patients by age, sex, and race.

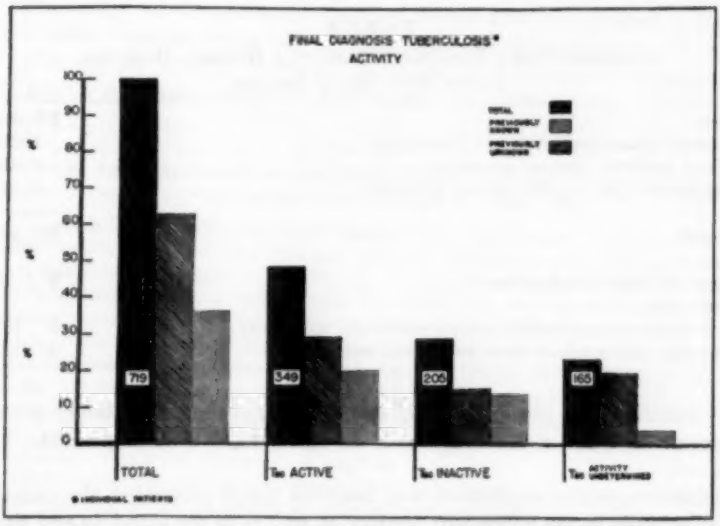

FIG. 6. Prevalence of active and newly discovered tuberculosis.

TABLE 5

ADMISSION CHEST ROENTGENOGRAMS AT A GENERAL HOSPITAL

Tuberculosis in Admissions to Los Angeles County Hospital

	FINAL DIAGNOSIS TUBERCULOSIS		COMPUTED TUBERCULOSIS*	
	Number	Prevalence per Thousand	Number	Prevalence per Thousand
Total tuberculosis, 34,040 persons examined	719	21	1,039	31
Tuberculosis previously unknown; all stages of activity	457	14	660	20
Active tuberculosis, previously known or unknown	349	10	501	15
Active tuberculosis, previously unknown	208	6	300	9

* Includes estimated tuberculosis in those referred to health departments.

compares rather favorably with the reported cost per case of $808 in the Los Angeles County mass roentgenographic survey. When the total computed tuberculosis is taken into account, the cost of discovering a case of previously unknown active tuberculosis is $125.

SUMMARY

The administration, operating procedures, and results of the first year of the routine admission chest roentgenographic program at the Los Angeles County Hospital, with a capacity of 3,413 beds, are discussed.

TABLE 6

ADMISSION CHEST ROENTGENOGRAMS AT A GENERAL HOSPITAL

Cost of First Year of Program

Salaries	$29,285
Equipment (amortized over ten years)	1,935
Overhead (utilities, janitor, et cetera)	2,000
Miscellaneous (film, repairs, forms, et cetera)	4,350
Total	$37,540
Cost per minifilm examination	$ 0.76
Cost per case	
Final diagnosis active tuberculosis previously unknown	$ 180
Computed active tuberculosis previously unknown	$ 125

The examinations were conducted continuously, twenty-four hours per day and seven days per week. Patients of all age groups, including infants, were examined.

Photofluorographic equipment was installed which permitted the examination of patients in the recumbent position as well as in the standing and sitting positions. A special stretcher was designed which could be used for general hospital purposes and also as a radiographic table in order to facilitate the examination of seriously ill or injured patients.

The minifilm report was delivered to the ward approximately twenty-four hours after the patient had been admitted to the hospital.

In those cases in which the minifilm findings were strongly suggestive of active tuberculosis, the patient was placed in isolation until the diagnosis was disproved or the patient was transferred to the tuberculosis service. Patients with probably inactive or suspected tuberculosis were not isolated. A 14- by 17-inch film examination was automatically recommended in all cases in which a diagnosis of tuberculosis was suspected. Those patients who were discharged before this examination could be obtained were reported to, and followed by, the Health Department.

A total of 49,478 patients were examined, representing 63.6 per cent of the patients available. Since the special stretchers were acquired, the rate of examination has increased to 81.5 per cent.

A final diagnosis of tuberculosis was made in 719 persons (2.1 per cent). Previously unknown tuberculosis occurred in 457 patients (1.4 per cent). There were 349 (1.0 per cent) cases of active tuberculosis, of which 208 (0.6 per cent) were previously unknown.

Approximately half of the cases of tuberculosis occurred in white males more than forty years old. There were 26 cases in patients less than fifteen years old. The greatest prevalence (6.7 per cent) occurred in non-white males from thirty-one to forty years of age. The rate in white males (3.6 per cent) was almost the same as in non-white males (3.4 per cent). Tuberculosis was three times as frequent in white males as in white females, and four times as frequent in non-

white males as in non-white females. There was no marked difference in prevalence between white (2.2 per cent) and non-white persons (1.6 per cent).

The cost per minifilm examination was $0.76. The cost of diagnosing a case of active, previously unknown tuberculosis was $180.

SUMARIO

El Plan de Admisión Sistemática para Radiografías Torácicas en el Hospital del Condado de Los Angeles: Informe para el Primer Año

Discútense aquí la administración, los métodos de funcionamiento y los resultados alcanzados durante el primer año del plan de admisión sistemática para radiografías torácicas en el Hospital del Condado de Los Angeles, dotado de una capacidad de 3,413 camas.

Los exámenes fueron llevados a cabo continuamente, veinticuatro horas al día y siete días por semana, comprendiendo enfermos de toda edad, incluso lactantes.

Los aparatos roentgenofotográficos instalados permitían examinar a los enfermos recostados así como en las posiciones erguida y sedente. Se fabricó una camilla especial que podía usarse para las tareas generales del hospital e igualmente como mesa de radiografía a fin de facilitar el examen de los sujetos enfermos de gravedad o lesionados.

El informe relativo a la minipelícula era entregado a la sala unas veinticuatro horas después del ingreso del enfermo en el hospital.

En los casos en que los hallazgos minirradiográficos sugerían poderosamente la existencia de tuberculosis activa, se aislaba al enfermo hasta confutar el diagnóstico o trasladar al sujeto al servicio de tuberculosis. No se aislaba a los enfermos que tenían probable tuberculosis inactiva o que eran meramente sospechosos. Recomendábase automáticamente radiografías de 35 x 42.5 cm. en todo caso en que se sospechaba existencia de tuberculosis. Los enfermos dados de alta antes de poder hacer dicho examen eran denunciados al, y seguidos por el, Departamento de Sanidad.

Se examinó a un total de 49,478 enfermos, representando 63.6 por ciento de los disponibles. Desde la adquisición de las camillas especiales, la proporción de exámenes ha aumentado a 81.5 por ciento.

Se hizo un diagnóstico definitivo de tuberculosis en 719 personas (2.1 por ciento). Descubrióse tuberculosis antes desconocida en 457 (1.4 por ciento). Hubo 349 casos (1.0 por ciento) de tuberculosis activa, 208 (0.6 por ciento) de los cuales eran desconocidos antes.

Aproximadamente la mitad de los casos de tuberculosis fueron en varones blancos de más de cuarenta años de edad. Hubo 26 casos en sujetos de menos de quince años de edad. La frecuencia máxima (6.7 por ciento) correspondió a varones que no eran de raza blanca de treinta y uno a cuarenta años de edad. El coeficiente en los varones blancos (3.6 por ciento) fué casi idéntico que en los que no eran blancos (3.4 por ciento). La tuberculosis fué tres veces más frecuente en los varones blancos que en las mujeres blancas, y cuatro veces más frecuente en los varones que no eran de raza blanca que en las mujeres que no pertenecían a dicha raza. No hubo mayor diferencia en frecuencia entre las personas que eran de raza blanca (2.2 por ciento) y las que no lo eran (1.6 por ciento).

El costo de cada examen minirradiográfico fué de $0.76. El costo del diagnóstico de un caso de tuberculosis activa, desconocida antes, representó $180.

RESUME

Un programme d'examen radiographique systématique du thorax après admission au Los Angeles County Hospital: Rapport sur la première année d'exercice

Etude sur l'administration, les procédés opératoires et les résultats de la première année de l'exécution d'un programme d'examen radiographique systématique du thorax après hospitalization au Los Angeles County Hospital. Cet hôpital a une capacité de 3.413 lits. Les examens étaient effectués de facon continue, vingt-quatre heures par jour et sept

jours par semaine. Des malades appartenant à tous les groupes d'âge, y compris les nourrissons, étaient examinés.

Un appareillage photo-radiographique permettant l'examen des malades en position couchée comme en position debout ou assise fut installé. Un brancard spécial, utilisable aussi bien pour le service d'un hôpital que comme table d'examen radiologique, a été construit pour faciliter l'examen des malades gravement atteints ou blessés.

Le rapport sur microfilm était remis au service intéressé vingt-quatre heures après l'admission du malade à l'hôpital. Dans les cas où les images du microfilm suggéraient le diagnostic de tuberculose en activité, le malade était isolé jusqu'à ce que le diagnostic soit infirmé ou que le malade soit transféré dans le service de la tuberculose. Les cas douteux dans lesquels la tuberculose paraissait inactive ou latente n'étaient pas isolés. Un cliché sur film de 14/17 était systématiquement effectué dans tous les cas où le diagnostic de la tuberculose latente ou probable était posé. Les malades, quittant l'hopital avant cet examen étaient signalés au Département de la Santé publique qui poursuivait l'observation.

Au total, 49.478 malades ont été examinés soit 63,6% des malades disponibles à ce moment. Depuis l'acquisition des brancards spéciaux le taux des examens a atteint 81,5%.

A la suite de ces examens, le diagnostic de tuberculose a été établi chez 719 individus (2,1%). Le diagnostic de tuberculose, antérieurement non reconnue, a été fait chez 457 sujets (1,4%). Il y avait 349 (1%) cas de tuberculose en activité, dont 208 (0,6%) étaient antérieurement non reconnus.

Approximatiquement la moitié de ces cas de tuberculose concernaient l'homme de race blanche âgé de plus de quarante ans. Vingt-six malades avaient moins de quinze ans. La prédominance la plus élevée (6,7%) apparaissait chez les sujets mâles de trente-et-un à quarante ans, la race blanche exceptée. Chez le blanc de sexe masculin, le taux (3,6%) était sensiblement le même que celui observé pour le même sexe dans les autres races, (3,4%). Dans la race blanche, la tuberculose était trois fois plus fréquente chez l'homme que chez la femme; dans les autres races elle était quatre fois plus fréquente chez l'homme que chez la femme. Il n'y avait pas de différence sensible de prédominance entre la race blanche (2,2%) et les autres races (1,6%). Le prix de revient d'un examen sur microfilm était de 0,76 dollars US. Le cout de l'examen diagnostique d'un cas de tuberculose active révélé par le programme de dépistage était de 180 dollars.

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EFFECTS OF HIGH DOSES OF ISONIAZID IN MAN[1,2]

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INTRODUCTION

The pharmacology and the acute and chronic toxicity of isoniazid have been described in a number of animal species, including the dog (1, 2) and the monkey (3, 4), and striking differences between these species have been observed. The acute LD_{50} dose for the dog by single intravenous injection is 50 mg. per kg., with death due to convulsions, and the chronic orally tolerated dose is 10 mg. per kg. per day (2). In contrast, Schmidt (3) found the acute convulsive single dose for the monkey to be greater than 80 mg. per kg., and the compound was well tolerated in a dosage of 20 mg. per kg. per day orally for periods of longer than seven months.

The usual dosage schedule employed in man in clinical studies of isoniazid as an antituberculous agent is 3 to 5 mg. per kg. per day (5-7), but doses as high as 20 mg. per kg. per day have been given (8). Systematic exploration and appraisal of human tolerance for higher dose levels of isoniazid, however, have not been reported. The present report is concerned with experiences with relatively large doses of isoniazid in the course of a study of this compound in neoplastic disease.

PLAN OF INVESTIGATION

The patients treated were 3 adults with far advanced lymphoma, one child with extensive neuroblastoma, and one patient with disseminated sarcoidosis. They were hospitalized during the period of study. Isoniazid was started in divided daily doses of 5 to 10 mg. per kg., and the dosage was increased in all cases to levels as high as 20 to 37.5 mg. per kg. per day. These levels were maintained for periods of six to seventy days (table 1).

The patients were examined daily for evidences of toxicity and for clinical response. Hemograms (hemoglobin level and leukocyte counts daily; and platelets, reticulocyte counts, and hematocrit once a week) were obtained in all cases, and serial blood chemical determinations were performed in 3 cases. These included: blood urea nitrogen, serum bilirubin, serum cholesterol and esters, alkaline phosphatase, prothrombin time, total protein and albumin-globulin ratios, cephalin flocculation, and thymol turbidity. Urine analyses were obtained at weekly intervals. Chemical assay of plasma concentrations of isoniazid were made by the technique of Kelly and Poet (9). These determinations were

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TABLE 1

CLINICAL DATA ON PATIENTS WHO RECEIVED ISONIAZID THERAPY

CASE NUMBER	AGE AND SEX	DISEASE	TOTAL DOSE		PERIOD OF THERAPY AT HIGHEST DAILY DOSE		TOTAL NUMBER DAYS OF THERAPY	TOXICITY	
			Gm.	Gm. per Kg.	Mg. per Kg. per Day	Duration		Clinical	Laboratory
						days			
1	28 F	Sarcoidosis	138.40	(3.45)	37.5	70	140	Paresthesias	0
2	32 F	Hodgkin's disease	61.40	(1.53)	25.0	54	69	0	0
3	69 M	Hodgkin's disease	22.80	(0.40)	25.0	6	21	0	0
4	65 F	Lymphosarcoma	15.75	(0.33)	25.0	6	19	0	0
5	2 3/4 M	Neuroblastoma	2.25	(0.15)	20.0	6	9	0	0

made primarily to detect evidence of accumulation of the drug on continued administration. Necropsies were performed on 4 patients who died three days to eighteen months after their course of isoniazid.

RESULTS

None of the 4 patients with neoplastic disease showed tumor regression or clinical improvement on isoniazid, and no subjective or objective evidence of toxicity to the drug was noted. The case of Boeck's sarcoid is presented in detail below (*Case 1*). The drug was well received by all of the patients. There were no significant alterations in the various laboratory tests that were performed. Random determinations of isoniazid plasma concentrations showed that significant concentrations of the drug were obtained in all cases, and no evidence of accumulation of the drug was noted (figure 1).

Necropsies performed on the 4 patients who died of their disease showed no gross or microscopic evidence of tissue injury which could be attributed to isoniazid.

The following case report is presented in detail because of the development of toxic manifestations to the drug.

Case 1. E. W., a 27-year-old Negro female, was admitted to the James Ewing Hospital on January 21, 1953, with disseminated sarcoidosis of five years' duration. Examination on admission showed a moderately well-nourished female who was dyspneic at rest. Generalized skin lesions of the lupus pernio and Boeck type were present, as well as hepatosplenomegaly. Roentgenogram of the chest showed extensive pulmonary infiltrations. After the initial laboratory determinations, the patient was started on isoniazid in a divided daily dosage of 5 mg. per kg., on February 4, 1953. The dosage was rapidly increased in a stepwise manner until a dosage of 37.5 mg. per kg. (300 mg. five times daily) was attained seventy days after therapy was started (figure 2). Gradual regression of the skin lesions was noted until they were 20 to 30 per cent of the pretreatment size. There was no improvement in the other features of the disease. Isoniazid plasma determinations showed a concentration of 20.4 γ per ml. one hour after the last evening dose of 300 mg., with a fall in the concentration to 4.0 γ per ml. twelve hours later.

On April 28, 1953, thirteen days after the dose of isoniazid had been increased to 37.5 mg. per kg. per day, the patient noted the gradual onset of numbness in the hands, which

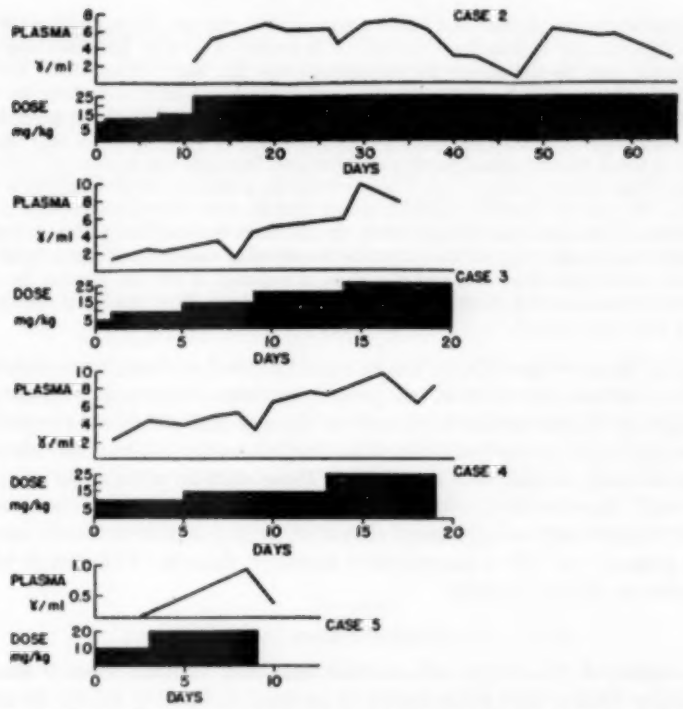

FIG. 1. Isoniazid dosages and plasma concentrations in *Cases 2 to 5*, inclusive.

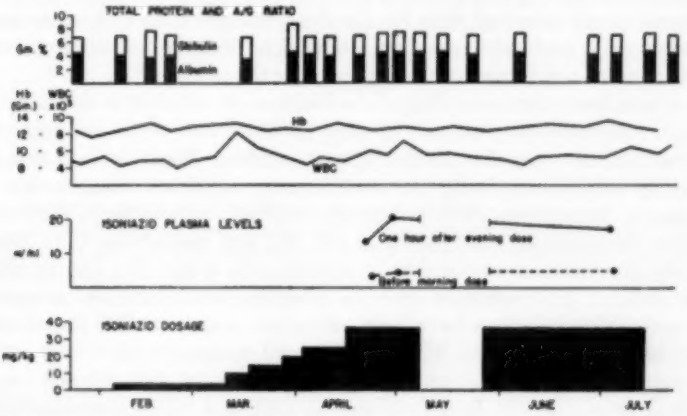

FIG. 2. Isoniazid dosage, plasma concentrations, and laboratory data in *Case 1*. Serial liver function tests (cephalin flocculation, thymol turbidity, alkaline phosphatase, cholesterol and esters, and prothrombin time) showed no alteration during therapy.

later spread to involve the feet and legs in a symmetrical manner. She complained of stiffness and tightening of the muscles of the calf and heaviness of the feet. Repeated neurologic examinations were normal except for hypesthesia over the distribution of the involved areas. There were no motor or reflex changes, and the patient was up and about the ward. Isoniazid was discontinued on May 7, 1953, nine days after the onset of the paresthesias.

The paresthesias gradually diminished during a two-week period and, by May 26, 1953, the patient noted only a residual numbness of the toes. Isoniazid was re-started at this time at the previous highest dosage level. The paresthesias gradually recurred during a three-week interval, and the drug was discontinued on July 13, 1953, after a total dosage of 138.4 gm. had been given during a 140-day period. At this time, the isoniazid plasma concentration was 17.0 γ per ml. sixty minutes after the last evening dose and had fallen to 5.1 γ per ml. fifteen hours later. Nicotinic acid was given in a dosage of 200 mg. per day for seven days without demonstrable effect on the neurologic symptoms. They gradually disappeared during a four-week period.

It is not possible to evaluate the therapeutic effect of isoniazid in this single case of sarcoidosis, inasmuch as unexpected remissions occur in this disease. The neurologic symptoms which developed on therapy and which were reproduced on a second course of the drug were of moderate severity, without residuals, and did not seriously incapacitate the patient. There were no withdrawal symptoms noted each time the drug was discontinued. Serial laboratory determinations (figure 2) failed to show significant alteration during or after isoniazid therapy. At the present time (three months after therapy), there is no clinical or laboratory evidence of drug toxicity.

DISCUSSION

The results of this study indicate that man may tolerate doses of isoniazid appreciably higher than those found to be fatal in the dog (1, 2). In *Case 1*, plasma concentrations of isoniazid were obtained which were twice those reported as lethal in the dog (2), and a dose of 37.5 mg. per kg. per day (almost four times the chronic orally tolerated dose for the dog) was given for as long as seventy days with only moderate toxic manifestations. Human tolerance, therefore, appears to more nearly approach that found in the monkey (3).

There have been numerous clinical observations of undesirable side effects and untoward reactions from isoniazid therapy (10-23). Most of the toxic manifestations reported are referable to the nervous system. These include peripheral neuropathy (which is probably the most common important complication (15)) nervousness, hyperexcitability, muscular twitching, hyperreflexia, difficulty in urination, constipation, toxic psychosis (10, 21), and convulsions (19). Many of these side effects were considered to be of autonomic origin (11), but no pharmacologic basis for this contention could be established in laboratory animals (17). Acute convulsive reactions have been prevented and controlled in animals by the use of barbiturates (18). Minor withdrawal symptoms have been reported to be common following discontinuance of the drug (10, 11). Allergic reactions (20), drug fever (13, 20), hemolytic anemia (10), and methemoglobinemia (14) have been noted. One case of reversible agranulocytosis has been reported (22).

In the vast majority of cases, however, the untoward reactions to isoniazid have not been of prolonged or serious consequence, and no consistent evidence of

parenchymal damage has been observed (5, 20). If warranted by therapeutic considerations, there appears to be no contraindication to a cautious and systematic exploration of high doses of isoniazid in man. In addition to the possible value of high doses of isoniazid in selected cases of tuberculosis, this drug has shown moderate *in vitro* activity against several fungi (24). The potentialities of isoniazid as an anti-fungal agent have not been clearly determined at high doses. McVay and Sprunt (25) have observed three cases of cervical-facial actinomycosis which benefited from isoniazid in doses as high as 18 mg. per kg. per day, and they emphasize the importance of large doses for anti-fungal activity.

SUMMARY

Five cases are presented in which isoniazid was administered in doses of 20 to 37.5 mg. per kg. per day and maintained at these levels for periods of six to seventy days without evoking any serious adverse reactions. Serial laboratory determinations showed no significant alterations, and necropsy in 4 patients failed to reveal tissue damage which could be attributed to the drug. The results suggest that human tolerance for isoniazid is greater than that which had been reported for the dog and may more closely approach the degree of tolerance reported for the monkey.

SUMARIO

Efecto de las Dosis Altas de Isoniacida en el Hombre

En los 5 casos presentados, se administró isoniacida a dosis de 20 a 35.5 mg. diarios por día, manteniéndose a esas cifras durante períodos de seis a setenta días sin provocar la menor reacción adversa. Las determinaciones de laboratorio en serie no revelaron alteraciones de importancia y las autopsias de 4 enfermos no mostraron lesiones histológicas que pudieran imputarse a la droga. Los resultados denotan que la tolerancia humana para la isoniacida es mayor que la descrita para el perro y puede acercarse más a la comunicada para el mono.

RESUME

Effets de hautes doses d'isoniazide chez l'homme

Présentation de cinq cas dans lesquels l'isoniazide fut administrée à la dose de 20 à 35.5 mg par kg par jour, ces doses étant maintenues pendant six à soixante-dix jours sans qu'il se produise aucune réaction d'intolérance importante.

Des examens de laboratoire en série n'ont révélé aucune anomalie significative et l'autopsie pratiquée chez quatre des malades n'a révélé aucune lésion imputable à l'isoniazide. Les résultats suggèrent que la tolérance de l'homme pour l'isoniazide est supérieure à celle qui a été déterminée chez le chien et elle se rapproche beaucoup plus du degré de tolérance observé chez le singe.

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THE USE OF PNEUMOPERITONEUM AS AN ADJUNCT TO THE PROLONGED STREPTOMYCIN–PARA-AMINOSALICYLIC ACID TREATMENT OF PULMONARY TUBERCULOSIS[1,2]

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INTRODUCTION

While prolonged streptomycin–para-aminosalicylic acid (PAS) treatment is proving very effective in many cases of pulmonary tuberculosis, failures are not uncommon in advanced disease, particularly when associated with cavities. The use of pneumoperitoneum in pulmonary tuberculosis, even as an adjunct to chemotherapy, continues to be a controversial subject (1). In an effort to assess its place in present-day streptomycin-PAS therapy, several Veterans Administration hospitals are currently engaged in a cooperative controlled study. While such a controlled study in prospect may be relatively free of the bias that may creep into a study in retrospect, the data provided by the latter may still prove useful in the final evaluation of the measure.

MATERIAL AND METHODS

The present report represents a retrospective analysis of a carefully selected series of patients, all of whom received prolonged streptomycin-PAS, and a portion of whom received simultaneous pneumoperitoneum.

In order to reduce the influence of other variables, the following criteria were adopted for the selection of cases:

The diagnosis of pulmonary tuberculosis must have been confirmed by the finding of *M. tuberculosis* in sputum or gastric washing cultures at some time.

The age must have been between twenty and fifty-five years.

There must have been one or more areas of rarefaction seen on the chest roentgenogram interpreted as cavity of 1 cm. or more in diameter.

The patient must not have received any previous antituberculous chemotherapy, collapse, or surgery.

Each patient must have received for at least eight months uninterrupted combined streptomycin, *1 gm. twice weekly*, and PAS, 12 gm. daily.

In patients who received pneumoperitoneum, inflation must have been initiated within *one* month of the start of chemotherapy, and a diaphragmatic rise of at least one posterior interspace measured on full inspiration chest roentgenograms must have been achieved.

No other surgical treatment, collapse, or chemotherapy must have been used during the eight-month observation period.

In order to obtain the largest possible number of patients who met these rather strict

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criteria, each case record of any patient admitted from January, 1951, on, who might have qualified, was reviewed not only at Trudeau Sanatorium but also at the Veterans Administration Hospital, Sunmount, New York. Despite the fact that several hundred cases were reviewed, only 66 met the criteria selected. Only 21 of these patients had been treated with pneumoperitoneum, mostly at Trudeau Sanatorium.

The patients were evaluated at three time periods: before the start of treatment, at the end of four months of treatment, and after eight months of treatment. The following factors were considered:

Number, size, and location of cavities. Size of cavity is expressed in centimeters and represents the average diameter of the largest cavity noted, not the total diameter of all cavities seen. The decision that all cavities had disappeared was confirmed in each instance by planigrams.

Bacteriology: sputum and gastric washing culture only. Culture "conversion" was considered to have been achieved after three or more consecutive sputum and/or gastric washing cultures were negative for *M. tuberculosis*.

Differences in proportions were tested for statistical significance by the Standard Error method. A difference which might have arisen from chance alone in no more than 2 per cent of cases was considered significant.

RESULTS

Disappearance of all cavities: The number of cavities present in any one patient had no apparent relation to the incidence and speed of disappearance of *all* cavities. Therefore, in assessing this factor, the largest cavity observed before treatment was used to classify each case.

Among patients who did *not* receive pneumoperitoneum, 40 per cent had achieved cavity disappearance by the end of the fourth month; 62 per cent, after eight months (table 1). In comparison, 62 per cent of the patients who *did* receive pneumoperitoneum had achieved cavity disappearance after four months; 86 per cent, after eight months. The gain in favor of pneumoperitoneum was thus approximately 40 to 50 per cent.

Considering only patients with cavities of 2 cm. or more, the gain in favor of pneumoperitoneum is approximately 90 per cent, a difference which proved statistically significant at eight months.

TABLE 1

INCIDENCE OF CAVITY DISAPPEARANCE AT FOUR AND EIGHT MONTHS OF TREATMENT AND OBSERVATION IN 66 PATIENTS ON STREPTOMYCIN–PARA-AMINOSALICYLIC ACID BY CAVITY SIZE AND USE OF PNEUMOPERITONEUM

DIAMETER OF LARGEST CAVITY	AT 4 MONTHS						AT 8 MONTHS					
	No Pneumoperitoneum			Pneumoperitoneum			No Pneumoperitoneum			Pneumoperitoneum		
	Cases	Cavity Disappearance		Cases	Cavity Disappearance		Cases	Cavity Disappearance		Cases	Cavity Disappearance	
		Number	Per Cent		Number	Per Cent		Number	Per Cent		Number	Per Cent
cm.												
1.0–2.0	19	12	63.2	12	8	66.6	19	16	84.2	12	10	83.3
2.1–4.0	19	6	31.6	8	5	62.5	19	10	52.6	8	7	87.5
4.1+	7	0	0	1	0	0	7	2	28.6	1	1	100.0
Totals...	45	18	40.0	21	13	61.9	45	28	62.2	21	18	85.7

TABLE 2

INCIDENCE OF CULTURE "CONVERSION" AT FOUR AND EIGHT MONTHS OF TREATMENT AND OBSERVATION IN 60 PATIENTS ON STREPTOMYCIN–PARA-AMINOSALICYLIC ACID BY CAVITY SIZE AND USE OF PNEUMOPERITONEUM

DIAMETER OF LARGEST CAVITY	AT 4 MONTHS						AT 8 MONTHS					
	No Pneumoperitoneum			Pneumoperitoneum			No Pneumoperitoneum			Pneumoperitoneum		
	Cases	Culture Conversion		Cases	Culture Conversion		Cases	Culture Conversion		Cases	Culture Conversion	
		Number	Per Cent		Number	Per Cent		Number	Per Cent		Number	Per Cent
cm.												
1.0–2.0	15	12	80.0	12	8	66.7	15	13	86.7	12	8	66.7
2.1–4.0	18	9	50.0	8	7	87.5	18	11	61.1	8	8	100.0
4.1+	6	2	33.3	1	1	100.0	6	2	33.3	1	1	100.0
Totals...	39	23	59.0	21	16	76.2	39	26	66.7	21	17	81.0

Reversal of infectiousness: Of the 45 patients who did *not* receive pneumoperitoneum, 39 were discharging tubercle bacilli immediately before treatment. Fifty-nine per cent of these were classified as noninfectious, i.e., negative for *M. tuberculosis* on culture, at four months; 67 per cent, at eight months. Of the 21 patients who received pneumoperitoneum plus chemotherapy, all were discharging tubercle bacilli before treatment. At four months of treatment, 76 per cent were noninfectious and, by the end of the eighth month, 81 per cent were noninfectious (table 2).

When the cases were analyzed by cavity size, it was seen that the differences in favor of pneumoperitoneum were confined to those patients with cavities of more than 2 cm. in diameter; these differences proved to be statistically significant at both four and eight months.

The significance of the location of cavity was also studied; there was no demonstrable relation between this factor and the speed and incidence of cavity disappearance.

DISCUSSION

Although this is a small series of cases, they were carefully selected according to rigid criteria. Moreover, as far as possible in any retrospective analysis, the influence of other important variables was held to a minimum. The group without pneumoperitoneum contained a higher proportion of patients with cavities of 2.1 cm. and over. In addition, while not all of the observed differences proved to be statistically significant, they were fairly large and consistent.

As measured by both cavity disappearance and reversal of infectiousness, the use of pneumoperitoneum apparently increased the effectiveness of twice weekly streptomycin–daily PAS treatment at both four and eight months of treatment and observation in the presence of cavitation of more than 2 cm. in diameter.

In those patients with 1.0 to 2.0 cm. cavities, however, there was no difference in the incidence of cavity disappearance, and there was a statistically insignificant difference in rate of reversal of infectiousness.

No information is available on the use of pneumoperitoneum with streptomycin regimens of 0.5 or 1.0 gm. *daily*; in re-treatment with or without the finding of streptomycin-and/or PAS-resistant tubercle bacilli; or in isoniazid regimens.

The speed of cavity disappearance is shown to have been greater with pneumoperitoneum than without it, regardless of cavity size (table 1). In addition, experience at Trudeau Sanatorium has suggested that pneumoperitoneum may be less effective when introduced three or four months after the start of streptomycin-PAS treatment rather than early in the course of such treatment. Hence, attention is called to the introduction of pneumoperitoneum during the first month in all patients included in this study.

If pneumoperitoneum increases the speed and/or incidence of cavity closure during streptomycin-PAS treatment, the risk of the emergence of drug-resistant bacilli may be materially reduced. This opinion is based upon the experience that streptomycin resistance is more apt to emerge in the presence of persistent air-containing cavity than when all lesions are or become closed (2).

SUMMARY

A retrospective analysis was made of 66 patients with cavitary pulmonary tuberculosis who were treated with streptomycin twice weekly and with para-aminosalicylic acid (PAS) daily.

Pneumoperitoneum with an appreciable diaphragmatic elevation had been introduced during the first month of chemotherapy in 21 of these patients. Judged by the incidence of cavity disappearance and reversal of infectiousness, as determined by culture, pneumoperitoneum had an apparently favorable influence on results at both four and eight months of treatment and observation of patients whose largest cavities measure 2 cm. or more in diameter.

SUMARIO

El Uso del Neumoperitoneo como Coadyuvante del Tratamiento Prolongado de la Tuberculosis Pulmonar con Estreptomicina-Acido Para-Aminosalicílico

Este análisis retrospectivo comprende a 66 enfermos que tenían tuberculosis pulmonar cavitaria y fueron tratados con estreptomicina dos veces semanales y con ácido para-aminosalicílico diariamente.

El neumoperitoneo, con una apreciable elevación diafragmática, fué introducido durante el primer mes de quimioterapia en 21 de esos enfermos. A juzgar por la incidencia de desaparición de las cavernas y de "viraje" del esputo y/o de los cultivos del lavado gástrico, el neumoperitoneo ejerció un efecto aparentemente favorable sobre los resultados observados al cabo tanto de cuatro como de ocho meses de tratamiento y observación en enfermos cuyas cavernas mayores medían 2 cm. o más de diámetro.

RESUME

Utilisation du pneumopéritoine comme adjuvant au traitement prolongé de la tuberculose pulmonaire par la streptomycine et l'acide para-aminosalicylique

Les auteurs font une analyse rétrospective de 66 cas de tuberculose pulmonaire cavitaire traités par la streptomycine deux fois par semaine et par l'acide para-aminosalicylique une fois par jour.

Un pneumopéritoine avec élévation diaphragmatique appréciable avait été instauré au cours du premier mois de la chimiothérapie chez 21 de ces malades. En prenant comme critère la fréquence de la disparition des cavernes et la négativation des crachats ou de l'expectoration prélevée par lavage gastrique après confirmation par l'examen direct ou par la culture, ou par les deux méthodes, le pneumopéritoine paraissait avoir influencé favorablement les résultats. Cette évaluation a été faite au bout de quatre à huit mois de traitement et d'observation de cas où le diamètre des cavernes les plus importantes atteignait deux centimètres ou plus.

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ARTIFICIAL PNEUMOTHORAX IN MIDDLE-AGED AND ELDERLY PATIENTS[1,2]

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INTRODUCTION

It seems to be generally agreed that pulmonary tuberculosis in middle-aged and elderly subjects lately has shown a relative increase in most countries of western civilization. Some of the increase is presumably attributable to more comprehensive case-finding programs. Whatever the causes, however, it is obvious that the greater number of persons in the older age groups known to have a chronic infectious disease poses problems both medical and social. The social consequences are too evident to require discussion here. The medico-therapeutic approach to the question involves consideration of the physiologic processes of aging. Healing of lesions, reversal of infectiousness, and restoration to working capacity are the desired goals in these as well as in younger patients.

Artificial pneumothorax, until recent years at least, has been a very widely used form of therapy for pulmonary tuberculosis in younger patients. Up to 1950 there were comparatively few reports of artificial pneumothorax in the older age groups (1–4). Since then several papers have been published.

Ehrner (5) described twenty patients with unilateral, and five with bilateral, pneumothorax. The patients were fifty-one or more years old, and the material covered the years from 1940 to 1949. In twelve cases "ideal collapse" was obtained. Naturally, treatment was still being maintained in some patients at the time of Ehrner's report. The writer formed the conclusion that "advanced age as such does not influence the results of artificial pneumothorax treatment." Leech (6) reported his experiences with artificial pneumothorax in patients more than fifty years old. Treatment was satisfactorily concluded in one case and was being successfully maintained in three others at the end of the observation period (1935 to 1945). Paul (7) attempted pneumothorax in 19 patients older than forty-five years, but in twelve had to abandon therapy because of contra-selective collapse or formation of an effusion. Sputum "conversion" was obtained in only one patient and, in this patient, pneumothorax was supplemented by pneumoperitoneum. Bondi and Leiner (8) described seventeen patients aged fifty to sixty-four years in whom pneumothorax was initiated between 1939 and 1945. Therapy was discontinued electively in only two patients; in the others a variety of complications necessitated its premature termination. Sputum "conversion" which could be attributed to the pneumothorax was achieved in five patients. These writers stressed the importance of immediate abandonment of an ineffective pneumothorax in older patients, and stated that, given good collapse and sputum "conversion," the long-term results appeared to be as satisfactory as in

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younger patients. It should be remarked that no less than ten of the seventeen patients had diabetes mellitus. Bérard, Ode, and Moulin (9), writing of tuberculosis in patients fifty years old, mentioned 108 pneumothoraces. In fifty cases, treatment had to be abandoned early for various reasons. Satisfactory and lasting results were claimed in fifteen cases but, unfortunately, no criteria were stated. The patients treated since 1951 had been given streptomycin and para-aminosalicylic acid (PAS) concurrently. Although artificial pneumothorax was not considered to be implicitly contraindicated in older patients, pessimism was expressed concerning the frequency of contra-selective collapse and complications. Manser (10) reported cavity closure from pneumothorax therapy in six patients older than sixty years treated between 1941 and 1951.

The comparative scarcity of reports on the treatment of tuberculosis in patients in the older age groups has prompted a study of the active therapeutic measures carried out at Söderby Hospital. The present paper concerns artificial pneumothorax.

CLINICAL MATERIAL

In the period from 1938 to 1952, 61 artificial pneumothoraces were instituted at Söderby Hospital in 58 patients older than fifty years. The total number of such patients admitted during that period was 1,465. Söderby is the pulmonary tuberculosis hospital for the city of Stockholm, and its patients represent all strata of the population. The proportion of patients more than fifty years of

TABLE 1

NUMBER OF PATIENTS MORE THAN FIFTY YEARS OF AGE ADMITTED TO SÖDERBY HOSPITAL FROM 1938 TO 1952, AND FREQUENCY OF ACTIVE THERAPEUTIC MEASURES

YEAR	PATIENTS OLDER THAN 50		ARTIFICIAL PNEUMOTHORAX	EXTRAPLEURAL PNEUMOTHORAX	PNEUMOPERITONEUM	PHRENIC CRUSH	THORACOPLASTY	RESECTION OPERATIONS	PULMONARY DECORTICATION
	Number Admitted	Per Cent of Total Adult Admissions							
1938	39	4.9	2 (5.1%)			1 (2.6%)			
1939	59	6.8	5 (8.5%)						
1940	77	8.6	3 (3.9%)				1 (1.3%)		
1941	57	6.1	5 (8.8%)				1 (1.7%)		
1942	68	7.0	3 (4.4%)						
1943	81	8.0	8 (9.9%)				1 (1.2%)	1 (1.2%)	
1944	71	8.0	3 (4.2%)				1 (1.4%)		
1945	90	9.0	4 (4.4%)				3 (3.3%)		
1946	83	8.5	2 (2.4%)				2 (2.4%)		
1947	94	11.4	2 (2.1%)						
1948	116	13.5	6 (5.2%)			1 (0.9%)	5 (4.3%)		
1949	120	13.2	6 (5.0%)	1 (0.8%)			3 (2.5%)	1 (0.8%)	
1950	143	15.2		1 (0.7%)			8 (5.6%)		
1951	163	15.9	6 (3.7%)	2 (1.2%)	1 (0.6%)		8 (4.9%)	3 (1.8%)	
1952	204	19.3	6 (2.9%)		2 (1.0%)		4 (2.0%)	5 (2.4%)	1 (0.5%)

age increased from 4.9 per cent of adult admissions in 1938 to 19.3 per cent in 1952 (table 1).

Cases in which pneumothorax was attempted but no space found are not included in this series. The distribution of the clinical material according to age and sex is shown in table 2.

Pulmonary tuberculosis had been diagnosed before the age of fifty in only 17 of the 58 patients and, in 6 of these, the contralateral lung had been treated with pneumothorax. An additional 2 patients had had exudative pleurisy in earlier life.

Of the 3 patients in whom bilateral pneumothorax was established after the age of fifty, one had both lungs treated concurrently and, in the others, the first pneumothorax was discontinued before the second was induced.

Cavitation was present in the treated lung in all but 7 cases. Tubercle bacilli were found in the sputum on microscopy in all but 2 patients, one of whom had tubercle bacilli in the sputum and the other in the gastric washings, as demonstrated by culture. The contralateral lung showed no active infiltration in 24 patients, active infiltration in 30, and cavitary disease in 7 patients (table 3).

Seventeen patients received antimicrobial drugs prior to induction of pneumothorax.

RESULTS

A general survey of the series of pneumothoraces is presented in table 4.

As the study covered fifteen years, during which time indications for the

TABLE 2

AGE OF PATIENTS AT TIME OF PNEUMOTHORAX INDUCTION

AGE IN YEARS	MALES	FEMALES	TOTAL
50 to 54	36	8	44
55 to 59	11	3	14
60 to 64	3	0	3
Total	50	11	61

TABLE 3

RELATIONSHIP OF THE CONDITION OF THE CONTRALATERAL LUNG AT PNEUMOTHORAX INDUCTION TO PROGNOSIS IN PATIENTS MORE THAN FIFTY YEARS OF AGE

CONTRALATERAL LUNG	TOTAL	ALIVE March 31, 1953		DEAD Tuberculosis		DEAD Nontuberculous Causes	
		Number	Per Cent	Number	Per Cent	Number	Per Cent
No active disease	24	17	70.8	4	16.7	3	12.5
Active infiltration	30	17	56.7	10	33.3	3	10.0
Cavitary disease	7	1	14.3	6	85.7		

TABLE 4

GENERAL SURVEY OF PNEUMOTHORAX THERAPY IN PATIENTS MORE THAN FIFTY YEARS OF AGE

YEAR	TOTAL OF PNEUMOTHORACES INDUCED	ELECTIVELY DISCONTINUED	PREMATURELY ABANDONED	MAINTAINED
1938	2	2 (2)		
1939	5	3 (2)	2	
1940	3	2	1 (1)	
1941	5	4 (1)	1	
1942	3	3 (2)		
1943	8	2 (1)	6	
1944	3		3 (1)	
1945	4	2 (2)	2	
1946	2	1 (1)	1 (1)	
1947	2		2 (2)	
1948	6	3 (2)	3	
1949	6		5 (4)	(1)
1950	0			
1951	6		3 (3)	(3)
1952	6		1 (1)	(5)
Total.....	61	22 (13)	30 (13)	(9)

The figures in parentheses denote the number of patients alive on March 31, 1953.

Six patients died of nontuberculous causes, one after pneumothorax was electively discontinued.

Seven of the 13 survivors with prematurely abandoned pneumothorax have since been treated surgically.

method have varied, it was considered that those cases in which treatment could be completed would provide the most satisfactory basis for an evaluation of artificial pneumothorax in older subjects.

Electively discontinued pneumothoraces: The electively discontinued pneumothoraces will be considered first. The minimum duration of therapy in the 22 cases of this group was three years. No patient received antimicrobial therapy prior to induction of pneumothorax.

One patient died of cerebral hemorrhage four weeks after his last refill and without sign of activity of the tuberculous disease. There were 8 deaths from progressive pulmonary tuberculosis (table 5). Thirteen patients were alive at the end of the observation period (March 31, 1953); the follow-up period ranged from less than one year to more than ten years after the last refill. In 10 of these 13 patients, the chest roentgenograms showed healed lesions, and gastric washings or concentrated specimens of sputum were negative for tubercle bacilli. All but one had had cavitary disease of the homolateral lung when pneumothorax was initiated. In all of the other 3 patients, reactivation of the lesions took place approximately four years after refills were discontinued.

Serous pleural effusion (covering the dome of the diaphragm) formed in 9 pneumothoraces, and mixed bacterial empyema in 2. In 6 cases there was contralateral spread of the disease during pneumothorax therapy. One patient had

TABLE 5

DURATION OF PNEUMOTHORAX THERAPY IN PATIENTS MORE THAN FIFTY YEARS OF AGE IN RELATION TO SURVIVAL AFTER ITS DISCONTINUATION

DURATION OF PNEUMOTHORAX	DEATH FROM TUBERCULOSIS AFTER (YEARS)					STILL ALIVE AFTER (YEARS)									TOTAL
	<1	1–2	2–3	7–8	Total	<1	1–2	2–3	3–4	4–5	5–6	7–8	8–9	9–10	>10	
Pneumothorax Prematurely Abandoned																
Less than 1 year	3				3	1	1	1	3 (3)		2 (2)					8 (5)
1–2 years	6		2		8	2 (1)				1		1				4 (1)
2–2½ years		1			1										1 (1)	1 (1)
Total.....	9	1	2		12	3 (1)	1	1	3 (3)	1	2 (2)	1			1 (1)	13 (7)
Pneumothorax Electively Discontinued																
3–4 years	1	2	2	1	6	1			2		1	2		1		7
4–5 years		1	1		2	1						1	1		2	5
5–6 years								1								1
Total.....	1	3	3	1	8	2		1	2		1	3	1	1	2	13

The figures in parentheses denote the number of patients since treated by surgery.
This table does not include the 6 patients who died of nontuberculous causes.

cardiac distress. In only 6 patients was the pneumothorax entirely free from complications. Five of these are alive and well; the sixth was the patient referred to above, who died of cerebral hemorrhage.

In no case was it possible to carry out tests of pulmonary function both before and after an electively discontinued pneumothorax. But study of the roentgenograms showed that some degree of pulmonary "contraction" was common and was sometimes a very prominent feature of therapy.

Prematurely abandoned pneumothoraces: The pneumothorax was prematurely abandoned in 30 patients. The maximum duration of therapy in these cases was two and one-half years. In distinguishing *electively discontinued* from *prematurely abandoned* pneumothorax, no requirements were set for the period of collapse, the opinion of the physician in charge of each case being the factor which decided assignment to the groups.

Nine of the 30 pneumothoraces were initiated after 1948 and were preceded by a period (not less than five weeks) of therapy with antimicrobial agents.

Premature abandonment of the pneumothorax was necessitated by serous pleural effusion in 6 cases, by tuberculous empyema in 3, and mixed bacterial empyema in 5 cases. Other reasons for abandonment were inadequate pleural space in 9 cases, persistent cavity in 3, contralateral spread of the disease in one case, and cardiac failure in one case.

Two patients died of pulmonary embolism from a blood clot in the femoral vein, one four days after induction of pneumothorax and one following open pneumonolysis. In 3 others, the respective primary causes of death were carci-

noma of the colon, arteriosclerosis, and hepatic cirrhosis. There were 12 deaths from progressive tuberculosis (table 5). Thirteen patients were alive on March 31, 1953, after observation periods ranging from less than one year to approximately ten years after the last refill. Seven of these 13 patients underwent thoracoplasty or pulmonary resection after abandonment of the pneumothorax. Of the remaining 6 patients, only 2 showed roentgenographic healing and sputum "conversion."

Survival time: Comparison of the survival time after elective and premature discontinuation of pneumothorax refills is made in table 5. It is seen that, of the 8 deaths from tuberculosis in the former group, only one occurred during the first year after therapy was terminated. The corresponding figures for the latter group are 12 and 9. The number of pneumothoraces electively discontinued at a time permitting survival for at least five years (before March 31, 1948) was 16. Eight of these patients were alive on March 31, 1953. Six of them showed healed pulmonary lesions and negative bacillary findings. After elimination of 3 patients who died of nontuberculous causes, 14 pneumothoraces were prematurely abandoned before the first date. Only 4 patients of this group are living, and, of these, 3 have undergone thoracoplasty.

Nine pneumothoraces were still being maintained when the study was concluded. Eight of the patients received preinduction medication with antimicrobial drugs. Three of the pneumothoraces have been complicated by serous effusion, but none by empyema.

The prognostic significance of the state of the contralateral lung is shown in table 3. The mortality figures were in direct proportion to the severity of the contralateral lesions.

A survey of the complications of artificial pneumothorax in the total series of cases is presented in table 6.

Adhesion section: Adhesion section was attempted in 34 cases, and the lung was thereby freed or selectively collapsed in 24 (table 7). Together with the cases in which adhesion section was not considered necessary, this group of satisfactorily collapsed lungs amounted to 32. Seven of the patients have died of progressive tuberculosis.

TABLE 6

COMPLICATIONS OF PNEUMOTHORAX THERAPY IN PATIENTS MORE THAN FIFTY YEARS OF AGE

	NUMBER	PER CENT OF PNEUMOTHORACES
Serous pleural effusion	15	24.6
Tuberculous empyema	3	4.9
Mixed bacterial empyema	7	11.5
Pulmonary embolism following induction of pneumothorax	1	
Pulmonary embolism following open pneumonolysis	1	
Cardiac failure	2	

TABLE 7

RELATIONSHIP OF THE QUALITY OF COLLAPSE TO PROGNOSIS IN PNEUMOTHORAX TREATMENT OF PATIENTS MORE THAN FIFTY YEARS OF AGE

QUALITY OF COLLAPSE	WITHOUT PNEUMONOLYSIS	AFTER PNEUMONOLYSIS	PNEUMOTHORAX TERMINATED				PNEUMOTHORAX MAINTAINED
			Number	Alive March 31, 1953	Dead of Tuberculosis		
					Number	Per Cent	
No visible adhesions	3	8	7	5	2	*28.6*	4
Selective	5	16	16	7	5*	*31.2*	5
Unsatisfactory	13	10	23	12†	11	*47.8*	
Total	21	34					

Pneumonolysis in this table indicates the *closed* procedure.

* Four additional patient with selective collapse died of nontuberculous disease.

† Seven of these patients were later treated surgically.

In the 23 cases in which satisfactory collapse was not obtained, there were 11 deaths from tuberculosis. It should be noted, however, that no less than 7 of the 12 survivors in this group have since been treated with thoracoplasty or lobectomy. These figures illustrate the value of good pulmonary collapse.

Open pneumonolysis: Five patients underwent open pneumonolysis, 3 of them after the closed procedure had failed. In all cases the operation was performed because of direct fusion of the visceral and parietal pleurae. One patient died of pulmonary embolism from a clot in the femoral vein four weeks after the operation. Empyema was the cause of death in 2 patients, five and nine months, respectively, after operation. The 2 surviving patients now show some pulmonary inexpansibility. In one of them, mixed bacterial empyema developed approximately a year after the operation and was successfully treated with antimicrobial agents.

Preinduction antimicrobial therapy: It is particularly rewarding to study the effect of antimicrobial drugs on the frequency of pleural complications in these older patients. Seventeen patients received, for at least five weeks prior to pneumothorax induction, 10 gm. of para-aminosalicylic acid (PAS) daily in the form of coated granules, or 1 gm. of streptomycin daily or thrice weekly, or combined PAS and streptomycin medication.

Serous pleural effusion covering the dome of the diaphragm appeared in 5 of the 17 patients, but purulent effusion was not seen. Of the 43 patients who did not receive such premedication, 10 had serous effusion and no less than 10 had empyema (table 8).

Antimicrobial agents, therefore, did not effect a reduction in the frequency of pleural effusion, although the figures are too small to be truly significant. The figures for empyema, on the other hand, are probably significant. But it must be remarked that the groups with and without preinduction medication may not be fully comparable; antimicrobial agents and the progress of surgery have

TABLE 8

PLEURAL EFFUSION AND EMPYEMA IN PNEUMOTHORAX PATIENTS MORE THAN FIFTY YEARS OF AGE

(Showing the Effect of Preinduction Treatment with Antimicrobial Agents on the Frequency of These Complications)

	NUMBER OF PNEUMOTHORACES	SEROUS EFFUSION	EMPYEMA
Premedication	17	5	0
No premedication	43*	10	10†

* The patient who died after induction of pneumothorax is not included.

† Includes 2 cases in which empyema followed open pneumonolysis.

changed the indications for artificial pneumothorax; if complications threaten, one is less reluctant than formerly to abandon a pneumothorax in favor of surgical intervention; and in some cases it is possible to prevent or treat inflammatory complications by means of local and/or systemic administration of antimicrobial agents.

DISCUSSION

Among tuberculous patients in the older age groups there is, of course, a fairly high percentage with old lesions which have reactivated or undergone acute progression. In such patients artificial pneumothorax is seldom indicated, since fibrous lesions rarely respond to temporary collapse of the lung. This has certainly been one cause of the relatively infrequent use of the method in patients more than fifty years of age at Söderby Hospital. Considering the small numbers involved, there has been little change in this respect from 1938 to 1952 (table 1). During these years, extrapleural pneumothorax, pneumoperitoneum, and phrenic crush have been used very infrequently. The number of thoracoplasties, on the other hand, showed a tendency to increase until 1950, when it began to diminish in favor of pulmonary resection.

Before the advent of antimicrobial therapy, the high risk of pleural complications in patients in the older age groups necessitated extreme caution in the decision to undertake pneumothorax therapy—another factor contributing to its low frequency. Mitchell (11), in a series of 605 cases of artificial pneumothorax initiated between 1930 and 1939 and followed in 1949, found that the incidence of empyema in patients sixteen to twenty-five years of age was 14.3 per cent; in patients twenty-six to thirty-three years, 18.4 per cent; and in those older than thirty-four years, it was 25.9 per cent. A mounting risk of pleural complications entails, of course, an increase in the frequency of inexpansibility of the lung after concluded pneumothorax. Added to this hazard there is, in the higher age groups, the reduction in pulmonary elasticity brought about by the normal processes of aging. And the danger of cor pulmonale is very real in such patients.

Since antimicrobial drugs became available, the risk of empyema has lessened. But with the progress of surgery, therapeutic pneumothorax has lost ground to plastic and resection operations. Thoracoplasty gives greater possibilities of

selective collapse in some cases and, consequently, of avoiding the contraction of the healthy parts of the lung which may follow pneumothorax. Resection of the diseased lung tissue also is often potentially less dangerous to respiratory function than pneumothorax.

On the other hand, the patient may be attracted by the thought of artificial pneumothorax as a less violent intervention. In cases in which the extent and type of the lesions hold out promise of satisfactory collapse, a trial of pneumothorax is justified. Nevertheless, the physician must be alert for any sign of complications so that, if necessary, the lung can be re-expanded and other therapy instituted.

In the older age groups, other diseases frequently have to be taken into account when forming a decision in regard to therapy for the tuberculous condition. Prominent among these is diabetes mellitus. In most middle-aged and elderly patients the presence of diabetes contraindicates artificial pneumothorax, chiefly because of the increased risk of empyema it entails. Only 3 patients in the present series had diabetes.

A few words must be said concerning open pneumonolysis. This operation was performed on 5 patients in the present series, with one surgical fatality and 2 deaths from empyema. As all 5 patients had direct fusion of the visceral and parietal pleurae, the high complication and death rates lend support to the dictum of Bruce and Crafoord (12) that open pneumonolysis should be reserved almost exclusively for "short, cord-type adhesions, where closed pneumonolysis implies manifest risk of pulmonary trauma or haemorrhage."

Although it is possible that the rapid advances now being made in the knowledge and treatment of pulmonary tuberculosis may relatively soon obviate any need for artificial pneumothorax in the higher age groups, it is too early as yet to discard the method entirely.

SUMMARY

A report is presented of 61 artificial pneumothoraces induced at Söderby Hospital during the period 1938 to 1952 in 58 patients more than fifty years of age.

In all but 7 patients there was cavitary disease of the treated lung. Direct sputum smears, sputum cultures, or gastric washings showed tubercle bacilli in every case.

Pneumothorax was terminated as an elective procedure in 22 patients. In 30 patients, it had to be abandoned prematurely, and in 9 it is still being maintained.

In the 22 cases of electively discontinued pneumothorax, refills were given for at least three years. One of these patients died of nontuberculous disease, and 8 of progressive tuberculosis. Of the 13 survivors, 10 showed roentgenographically healed lesions and sputum "conversion" at the end of the observation period (March 31, 1953).

In the 30 cases of prematurely abandoned pneumothorax, there were 2 deaths from pulmonary embolism, one after pneumothorax induction and one after

open pneumonolysis. Three other patients died of nontuberculous causes, and 12 of progressive tuberculosis. Of the 13 patients alive at the end of the observation period, 7 had undergone thoracoplasty or pulmonary resection. Only 2 of the other 6 showed pulmonary healing and negative bacillary findings.

The main reasons for premature abandonment of artificial pneumothorax were inadequacy of the pleural space, serous effusion, and empyema.

Other factors influencing the results of therapy were the state of the contralateral lung and the quality of the collapse.

Antimicrobial agents were given prior to induction of pneumothorax in 17 cases. There was no decrease in the frequency of serous effusion in these cases, compared with the 43 in which such medication was not given, but the number of pneumothoraces complicated by empyema fell from 10 to 0.

Although antimicrobial agents, by lessening the risk of empyema, might have been expected to widen the indications for artificial pneumothorax in the older age groups, the progress of thoracic surgery has made thoracoplasty or pulmonary resection preferable in some cases. Nevertheless, provided a careful watch is kept for complications which could damage respiratory function, artificial pneumothorax merits trial in middle-aged and elderly patients in whom the site and extent of the tuberculous lesions promise good selective collapse of the lung.

SUMARIO

El Neumotórax Terapéutico en las Personas de Edad Media y Avanzada

Versa esta comunicación sobre 61 neumotóraces terapéuticos inducidos en el Hospital Söderby durante el período transcurrido de 1938 a 1952 en 58 enfermos de más de cincuenta años de edad.

En todos ellos, menos 7, había afección cavitaria del pulmón tratado. Los frotes directos del esputo, los cultivos del esputo o los lavados gástricos revelaron bacilos tuberculosos en todos los casos.

El neumotórax fué terminado como procedimiento electivo en 22 enfermos, tuvo que ser abandonado prematuramente en 30 y se mantiene todavía en 9.

En los 22 casos de suspensión electiva del neumotórax, se hicieron reinsuflaciones a lo menos durante tres años. Uno de esos enfermos falleció de afección no tuberculosa y 8 de tuberculosis evolutiva. De los 13 sobrevivientes, 10 revelaron radiográficamente lesiones cicatrizadas y "viraje" del esputo al terminar el período de observación (31 de marzo de 1953).

Entre los 30 casos de abandono prematuro del neumotórax, hubo 2 muertes de trombosis embólica, una después de la inducción del neumotórax y una después de una neumonolisis abierta. Otros 3 enfermos fallecieron de causas no tuberculosas y 12 de tuberculosis evolutiva. De los 13 vivos al terminar el período de observación, 7 habían sido objeto de una toracoplastia o resección pulmonar. Dos solamente de los otros 6 mostraban cicatrización pulmonar y hallazgos bacilares negativos.

Las principales razones para el abandono prematuro del neumotórax artificial fueron insuficiencia del espacio pleural, derrame seroso y empiema.

Otros factores que afectaron los resultados de la terapéutica fueron el estado del pulmón contralateral y la calidad del colapso.

En 17 casos, administráronse agentes antimicrobianos antes de la inducción del neumotórax. No hubo disminución de la frecuencia del derrame seroso en estos enfermos, comparados con los 43 en que no se administró tal medicación, pero el número de neumotóraces complicados por empiema descendió de 10 a 0.

Aunque hubiera sido de esperar que los agentes antimicrobianos, por minorar el riesgo de empiema, ensancharan las indicaciones del neumotórax terapéutico en los grupos de mayor edad, el adelanto de la cirugía torácica hace que la toracoplastia o la resección pulmonar sean preferibles en algunos casos. No obstante, con tal que se mantenga una vigilancia cuidadosa a la mira de complicaciones que puedan lesionar la función respiratoria, el neumotórax artificial merece ser probado en los enfermos de edad media y avanzada, en los que el sitio y la extensión de las lesiones tuberculosas prometen buen colapso selectivo del pulmón.

RESUME

Pneumothoraz artificial chez les malades ayant dépassé cinquante ans

Présentation d'un rapport concernant 61 pneumothorax artificiels effectués au "Söderby Hospital" entre 1938 et 1952 chez 58 malades agés de plus de cinquante ans.

Chez tous les malades, sauf 7, il existait des cavernes dans le poumon traité. Dans tous les cas on trouvait le B.K. à l'examen direct du crachat, dans les cultures et dans le prélèvement par lavage gastrique.

Le pneumothorax fut terminé comme un procédé d'élection chez 22 malades. Chez 30 malades il a du être abandonné prématurément et chez 9 il est encore actuellement en cours.

Dans les 22 cas de pneumothorax électivement intermittent, les insufflations ont été périodiquement répétées pendant au moins trois ans. Un de ces malades est mort d'une affection non tuberculeuse et 8 de tuberculose évolutive. Parmi les 13 survivants, 10 présentaient des aspects radiologiques de cicatrisation et une "conversion" des crachats à la fin de la période d'observation (31 mars 1953).

Dans les 30 cas de pneumothorax abandonné prématurément, il y a eu 2 décès par thrombo-embolie, l'un après l'instauration du pneumothorax, l'autre après pneumolyse ouverte. Trois malades sont morts d'affections non tuberculeuses et 12 de tuberculose évolutive. Parmi les 13 malades qui étaient vivants à la fin de l'observation, 7 avaient subi une thoracoplastie ou une résection pulmonaire. Dans les 6 autres cas, la cicatrisation pulmonaire et les examens de laboratoire négatifs n'ont été obtenus que dans deux cas.

Les principales raisons qui ont justifié l'abandon du pneumothorax étaient les conditions inadéquates de l'espace pleural, l'épanchement séreux ou l'empyème.

Les autres facteurs intéressés dans le résultat de cette thérapeutique comprenaient l'état du poumon opposé et la qualité du collapsus.

Dans 17 cas, les agents antibactériens ont été administrés avant l'instauration du pneumothorax. Par comparaison avec les 43 cas privés de cette médication, aucune réduction de la fréquence des épanchements séreux n'a été observée chez ces sujets, mais le nombre des cas de pneumothorax compliqués d'empyème est tombé de 10 à 0.

Bien qu'on put espérer que les agents antibactériens, en diminuant le risque d'empyème, augmenteraient les indications du pneumothorax artificiel chez les malades âgés, les progrès de la chirurgie thoracique ont rendu la thoracoplastie ou la résection pulmonaire préférable dans certains cas. Cependant, en exerçant surveillance rigoureuse permettant de déceler l'apparition de manifestations risquant d'altérer la fonction pulmonaire, et lorsque le siège et l'étendue des lésions tuberculeuses permettent un bon collapsus sélectif du poumon, le pneumothorax artificiel mérite d'être tenté chez les malades d'âge moyen ou chez le vieillard.

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STREPTOMYCIN ONCE WEEKLY IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

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INTRODUCTION

When comparing various regimens employing streptomycin and daily para-aminosalicylic acid (PAS) in the treatment of pulmonary tuberculosis, it seems generally agreed that, in most cases, similar results may be obtained when the streptomycin is given either daily or twice weekly (1). Streptomycin administered at weekly intervals has been much less thoroughly studied.

The use of 2 gm. of streptomycin given once weekly, with daily PAS, was suggested to the present writers by a paper of Dr. Norma Furtos (2). In cooperation with other Veterans Administration hospitals (3), a pilot study was started, embodying this regimen. Patients for the once-weekly regimen were chosen by random selection from others who were to receive streptomycin twice weekly plus daily PAS. The present report describes the results with 209 patients treated with these two schedules.

PLAN OF INVESTIGATION

Ninety-six patients received 2 gm. of streptomycin one day a week (generally given in 4 cc. of solution, 2 cc. in each buttock at the same time). Three-fourths of this group of patients received, in addition, 16 gm. of sodium PAS daily, and one-fourth received oxytetracycline (Terramycin), 1 gm. daily orally, for the first four months of treatment. One hundred and thirteen patients, considered as a control group, received 1 gm. of streptomycin twice weekly. PAS and oxytetracycline were given to them in approximately the same proportions as to the patients who received 2 gm. of streptomycin one day a week. The patients who received PAS and those who received oxytetracycline have been considered together for reasons detailed later.

Selection of cases: The study was started in March, 1951. Every patient admitted to the hospital was assigned a register number in the admission office. If a patient was thought to require streptomycin treatment for pulmonary tuberculosis, he fell into this study; those with even register numbers were control cases (streptomycin, 1 gm. twice weekly), and those with odd numbers were placed on the once-weekly streptomycin regimen. The investigators had no control over which regimen would be used for a particular patient, nor any knowledge of which regimen the patient would receive until after the decision to administer streptomycin had been made.

Patients were excluded from the study when the following conditions were present:

Proved or probable bacterial resistance to streptomycin before starting chemotherapy. By streptomycin resistance is meant profuse growth (4-plus) of tubercle bacilli

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on a tube of solid medium containing 10γ of streptomycin per ml., equal to the growth obtained on a control tube containing no streptomycin. Patients were presumed to have bacterial resistance (even without laboratory proof), and were excluded from the study, if they had received streptomycin alone for any appreciable time before the study was begun, or if they had a history of failure to respond to streptomycin in the past or of a relapse while receiving streptomycin. An occasional patient was included at the start of the study but was removed when drug-susceptibility tests performed upon organisms obtained prior to treatment revealed them to be resistant to streptomycin.

Administration of a previous course of any antituberculous chemotherapy up to, or within one month of, the patient's admission to this hospital. This condition was considered a cause for exclusion from the study because it was believed that any response obtained while under treatment might be due, at least partially, to the effects of the previous course of chemotherapy.

Previous administration of isoniazid, for reasons similar to those mentioned above.

A history which suggested that the patient would not tolerate either streptomycin or PAS. The history might be one of febrile reaction, dermatitis, severe gastrointestinal intolerance, eighth-nerve damage, et cetera.

"Panic" cases. After isoniazid became available, 4 patients were excluded from the study because they were desperately ill; they were treated with streptomycin, PAS, and isoniazid.

Early in 1951, 21 consecutive patients with far advanced disease were treated with an experimental regimen consisting of streptomycin, 1 gm. twice weekly, and 5 gm. of oxytetracycline daily; they were excluded from the present study. (They should not be confused with the 62 patients referred to earlier, who received 1 gm. of oxytetracycline daily in place of PAS. The latter were randomized between the two streptomycin regimens and are included in the present study.)

The cases excluded from the study are tabulated in table 1. They were divided about equally between the two regimens.

The present report includes only those patients who completed four or more months of treatment. A number of patients who were started on one of the two randomized regimens discontinued treatment before four months had been reached. The reasons are listed in table 2. Both regimens were affected in a similar fashion.

As mentioned above, one-third to one-fourth of the patients in each group received oxytetracycline, 1 gm. daily, in place of PAS during the first four months of treatment. A change from oxytetracycline to PAS or from PAS to oxytetracycline was not considered as an interruption or a cessation of treatment. In a study (4) of 81 cases of pulmonary tuberculosis treated with streptomycin and oxytetracycline in this hospital, it was found that patients who received this combination of drugs showed approximately the same thera-

TABLE 1

PATIENTS WITH PULMONARY TUBERCULOSIS WHO RECEIVED CHEMOTHERAPY BUT WERE NOT INCLUDED IN THE STUDY

	EVEN REGISTER NUMBER	ODD REGISTER NUMBER
Streptomycin-resistant	17	15
Continuation of previous regimen	38	26
Known streptomycin or PAS intolerance	4	6
"Panic" cases	1	3
Special study (oxytetracycline, 5 gm. daily)	10	11
Total	70	61

TABLE 2

PATIENTS WHO COMPLETED LESS THAN FOUR MONTHS OF STREPTOMYCIN TREATMENT

	1 GM., TWICE WEEKLY	2 GM., ONCE WEEKLY
Irregular discharge	27	25
PAS toxicity or intolerance	1	4
Streptomycin toxicity or intolerance	0	4
Therapeutic failure	4	3
Death (nontuberculous)	3	0
Lack of cooperation	0	2
Transfer	0	1
Total	35	39

TABLE 3

ANALYSIS OF THE TWO GROUPS BY DEGREE OF DISEASE AND OTHER FACTORS

	STREPTOMYCIN, 2 GM. ONCE WEEKLY		STREPTOMYCIN, 1 GM. TWICE WEEKLY	
	Number	Per Cent	Number	Per Cent
Minimal	3	3	3	3
Moderately advanced	50	52	61	54
Far advanced	43	45	49	43
Original treatment	65	68	84	74
Re-treatment	31	32	29	26
Oxytetracycline* treatment	25	26	37	33

* Oxytetracycline, 1 gm. daily, instead of PAS for the first four months of treatment.

peutic results as those who received streptomycin and PAS. Similar results have also been reported from Fitzsimons Army Hospital (5). The oxytetracycline and PAS groups in the present study were analyzed separately, but the results were so similar that the figures were pooled.

The substitution of dihydrostreptomycin for streptomycin was not considered as an interruption or a cessation of treatment. The addition or substitution of amithiozone, pyrazinamide (Aldinamide), viomycin, or isoniazid was considered as equivalent to cessation of treatment under the terms of the present study.

Composition of the clinical material: All of the patients in the study were males. The cases were divided into extent of tuberculosis as follows: Streptomycin, 2 gm. once weekly: minimal, 3 per cent; moderately advanced, 52 per cent; far advanced, 45 per cent. Streptomycin, 1 gm., twice weekly: minimal, 3 per cent; moderately advanced, 54 per cent; far advanced, 43 per cent. The cases were divided into original treatment cases (patients who had received no previous streptomycin or less than thirty days of previous streptomycin therapy) and re-treatment cases (patients who had received more than thirty days of previous streptomycin treatment). These are tabulated in table 3.

Evaluation of results: There are various ways of measuring therapeutic efficacy in pulmonary tuberculosis. In the present study it was decided to disregard, in large part, the clinical picture as characterized by weight, fever, symptoms, et cetera. The two groups have been analyzed according to:

All degrees of roentgenographic improvement

Roentgenographic improvement great enough to be classified as moderate or marked in degree

"Conversion" of sputum to negative for tubercle bacilli

A combination of cavity closure (in patients with a cavity 2 cm. or more in diameter), stationary roentgenographic findings, and sputum "negativity," designated as "therapeutic target point reached" (6)

Achievements of inactivity (7)

All roentgenograms were interpreted by the present writers. At the time of roentgenographic interpretation, knowledge of the drug regimen used was not available. It was hoped that in this way subjective errors would occur about equally in both groups. This point is discussed in more detail later in the paper.

"Negative sputum," as used in this report, means that at least three consecutive forty-eight-hour sputum specimens failed to reveal *M. tuberculosis* upon microscopic examination after concentration and by culture; and, in addition, that three gastric washings or three further consecutive forty-eight-hour concentrated sputum specimens were also negative upon culture; and, finally, that no other specimens obtained at the same time yielded positive cultures. The diagnosis of cavity closure was generally based upon planigraphic evidence. The diagnosis of inactivity was based upon *Diagnostic Standards*, published by the National Tuberculosis Association, except that the diagnosis was usually made while the patient was still receiving chemotherapy.

Pneumoperitoneum, phrenic paralysis, or major surgery were used in those cases in which indications were thought to exist. These were used approximately equally in both groups and are not analyzed separately.

The cases were analyzed at four-, eight- and twelve-month end points. In evaluating therapeutic efficacy with a single regimen, a single end point may be desirable, for it is apparent that most patients will continue to improve with continued hospitalization and treatment and, especially, with continued chemotherapy. In comparing two concurrent regimens, it is important to be certain that a large number of poor results are not siphoned off early from one of the two regimens being studied, leaving only the good results to be tabulated at later end points. For this reason, all patients who stopped treatment after four months but in less than twelve months have been listed in table 4.

Patients still being continued on one of the two regimens are classified as "continuing treatment." It may be seen that both groups have had about equal numbers of cases dropped (and for similar reasons) after having had four or more months, but less than twelve months, of treatment. Patients classified

TABLE 4

REASONS FOR STOPPING TREATMENT* AFTER FOUR MONTHS BUT IN LESS THAN TWELVE MONTHS

	STREPTOMYCIN, 2 GM. ONCE WEEKLY			STREPTOMYCIN, 1 GM. TWICE WEEKLY		
	Original Therapy	Re-treatment	Total	Original Therapy	Re-treatment	Total
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Failure	12	16	13	8	17	11
Irregular discharge	24	28	25	24	35	27
Streptomycin toxicity or intolerance	2	0	1	3	0	2
PAS toxicity or intolerance	5	3	5	8	3	6
Planned course completed	10	3	7	17	10	14
Continuing treatment	47	50	49	40	35	40

* This includes patients continuing chemotherapy but removed from the study because of the addition of isoniazid, viomycin, amithiozone, pyrazinamide, et cetera.

as "planned course completed" were those whose disease was considered to be inactive, generally at the end of twelve months of continuous treatment.

RESULTS

The results of treatment are tabulated in tables 5 through 8. The cases were analyzed separately with respect to moderately advanced and far advanced disease, but the roentgenographic results were so similar that they were combined for table 5.

Roentgenographic findings: It may be seen, from the standpoint of roentgenographic changes, that at the end of four months the twice-weekly regimen showed a somewhat greater percentage of patients in the moderate and marked improvement classification, but that at eight and twelve months the results were similar with both regimens.

Bacteriologic findings: Sputum "conversion" figures are given separately for moderately and far advanced cases (tables 6 and 7). "Conversion" of sputum to negative for tubercle bacilli was noted in a large percentage of patients with moderately advanced disease treated with each regimen (table 6). Here, too, there is a suggestion of better bacteriologic results at the four-month point in the twice-weekly group. Thus, of 52 patients with sputum positive for tubercle bacilli at the start of treatment with streptomycin twice weekly, 33 per cent were positive at four months. In the streptomycin once-weekly group, 41 per cent of 39 originally positive were still positive for tubercle bacilli at four months. No differences could be seen at eight and twelve months, or at any point in the study of the far advanced cases except at the end of one year. At this point, 5 of 16 patients had sputum positive for tubercle bacilli in one group, and 3 of 15 patients in the other. It is not believed that any conclusions can be drawn from these few cases.

"Target-point" attainment: Within the larger group a number of patients were found to have "positive" sputum and cavitation of over 2 cm. in diameter and were designated as "target" cases. There were 25 such cases in the once-weekly group. At various periods of time (four to twelve months), 9 (36 per cent) reached the target (cavity closure, sputum "conversion," stationary lesions on roent-

TABLE 5

ROENTGENOGRAPHIC CHANGES

Moderately and Far Advanced Pulmonary Tuberculosis

	STREPTOMYCIN, 2 GM. ONCE WEEKLY						STREPTOMYCIN, 1 GM. TWICE WEEKLY					
	No Change or Worse		All Degrees Improvement		Moderate and Marked Improvement		No Change or Worse		All Degrees Improvement		Moderate and Marked Improvement	
	Number	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*	*Number*	*Per cent*
4 months	11	12	82	88	47	40	14	13	96	87	68	62
8 months	4	7	57	93	50	81	4	5	71	95	63	85
12 months	3	11	23	89	22	85	4	10	32	90	31	87

TABLE 6

MODERATELY ADVANCED CASES

Sputum Conversion (by Culture)

	STREPTOMYCIN, 2 GM. ONCE WEEKLY		STREPTOMYCIN, 1 GM. TWICE WEEKLY	
	Number	Per Cent	Number	Per Cent
Sputum positive* at start	39†/50	78	52/61	85
Sputum positive at 4 months	16/50	32	17/61	28
Sputum positive at 8 months	3/27	11	4/38	11
Sputum positive at 12 months	1/11	9‡	3/14	21‡

* For *M. tuberculosis* on smear or culture.

† Figures beneath the line give the total number of cases studied at the given point in time.

‡ Too few cases to be significant.

TABLE 7

FAR ADVANCED CASES

Sputum Conversion (by Culture)

	STREPTOMYCIN, 2 GM. ONCE WEEKLY		STREPTOMYCIN, 1 GM. TWICE WEEKLY	
	Number	Per Cent	Number	Per Cent
Sputum positive* at start	43†/43	100	45/49	92
Sputum positive at 4 months	32/43	74	34/49	70
Sputum positive at 8 months	15/27	56	16/31	50
Sputum positive at 12 months	5/12	31	3/15	20

* For *M. tuberculosis* on smear or culture.

† Figures beneath the line give the total number of cases studied at the given point in time.

genography, with or without the use of surgery). Fifteen (42 per cent) of the 35 target cases in the twice-weekly group reached the therapeutic target (table 8).

Undoubtedly, if each patient had received a minimum of twelve months of treatment, the results would have been much better. In table 8, some cases are

TABLE 8

CASES REACHING THE THERAPEUTIC TARGET POINT*

	STREPTOMYCIN, 2 GM. ONCE WEEKLY		STREPTOMYCIN, 1 GM. TWICE WEEKLY	
	Number	Per Cent	Number	Per Cent
"Target cases"	25	100	35	100
Reached	9	36	15	42
Failure	16	64	20	58

* Medically or after the addition of surgical measures.

reported at four months, others at eight, and still others at the twelve-month end point. However, in comparing the two regimens no appreciable difference can be seen.

In 29 (58 per cent) of the patients with moderately advanced disease in the 2 gm. once-weekly group, the lesions became inactive with or without surgery, compared to 34 (56 per cent) in the 1 gm. twice-weekly group. In 12 patients with far advanced disease (28 per cent), the lesions became inactive in the 2 gm. once-weekly group, compared with 18 (37 per cent) in the 1 gm. twice-weekly group. Here, again, the results would almost certainly have been better in both groups if each patient were reported at the end of one year of treatment.

Achievement of an inactivity status for the lesion by NTA standards (except for the fact that chemotherapy was being continued) was also achieved in about equal percentages in both regimens (58 per cent and 56 per cent in moderately advanced cases, 28 per cent and 37 per cent in the far advanced group).

By all of the above criteria, the two regimens gave approximately equal results at eight and twelve months, with a suggestive edge for the twice-weekly streptomycin at the four-month point.

Drug toxicity: Drug toxicity of a significant degree was not noted in either group. Patients who received 2 gm. one day a week were more likely to complain of flushing, headache, or paresthesia on the day of the injection. If this was pronounced, the dosage was dropped to 1 gm. and, in each case, successfully increased by 0.1 gm. weekly increments to the full dosage.

Drug-susceptibility tests: Streptomycin- and PAS-susceptibility tests were performed on all available cultures. All bacilli were susceptible to both drugs at the start of the study. At four months, in the once-weekly group, of 27 "positive" cultures, 4 (15 per cent) were resistant to streptomycin; at eight months, of 7 "positive" cultures, 2 were drug-resistant; and at twelve months, of 6 "positive" cultures, one was drug-resistant. In the twice-weekly group, there were 26 "positive" cultures at the end of four months; of these, 6 (24 per cent) were resistant to streptomycin. At eight months there were but 9 "positive" cultures, of which 4 were drug-resistant and, at twelve months, 2 were "positive" and one was drug-resistant.

Of 24 strains tested for drug susceptibility to PAS after four or more months of treatment in both groups, 2 strains were resistant at the end of four months

and one was resistant at eight months. The total number of resistant cases to either drug was small and so similar in the two groups that no differences were apparent. The low percentage of PAS resistance in the once-weekly group is perhaps of some special interest.

DISCUSSION

As streptomycin persists in the blood for twelve to twenty-four hours after an injection (8), the use of this drug every third day with excellent results would seem to indicate that its continued presence in the blood is not necessary. The optimum period between injections may depend upon various factors but, undoubtedly, therapeutic efficacy must be one of the most important. This present report attempts to compare the therapeutic value of two regimens in which the interval between the injections was the only variable by as objective criteria as were available.

When evaluating two concurrent therapeutic programs, some objective method of alloting the cases between them is advisable. In the present study, the register number by which the particular regimen was chosen was assigned before the patient was seen by any of the staff physicians. Moreover, as the therapy conference members in any case did not know the patient's register number when the decision to administer chemotherapy was made, it was believed that this method of randomization would avoid bias in the selection of cases. Many patients were excluded from the study on the basis of criteria previously agreed upon (*see* table 1). The decision to exclude a patient was made with no knowledge, at the time, of which regimen would otherwise have been used. It is believed that the excluded cases classified in table 1 reveal an absence of bias or coincidence unduly favoring either regimen.

The patients who completed less than four months of treatment, which constituted presumably bad results, fell equally into the two regimens (table 2). Cases classified as "therapeutic failure" prior to four months are of some interest. Three patients with far advanced disease who received 2 gm. once weekly were noted, at the end of two months, to show continuing daily fever of 101°F. or more. In each case there were evidences of roentgenographic and clinical improvement. All of these patients were removed from the study (and included as such in table 2) and were treated with 1 gm. of streptomycin daily, with daily PAS. In one instance the temperature dropped to normal almost at once; in the other 2 it persisted unchanged for one to two months longer. There were no similar cases in the control group.

The data in table 3 indicate that the cases were approximately equally distributed between the two regimens with respect to such factors as degree of disease, original treatment versus re-treatment, and administration of oxytetracycline instead of PAS during the first four months of treatment.

It is well recognized that roentgenographic interpretation is not so objective as might be wished (9). It is also appreciated that, when chemotherapy is started soon after admission to a hospital, changes for the better may be due to the natural course of the disease or to the effects of rest, pneumoperi-

toneum, surgery, et cetera, and not alone to the drugs employed. In addition, the distinctions between "slight," "moderate," and "marked" degrees of roentgenographic improvement are highly subjective. A small infiltrative lesion with a 2 cm. cavity might clear completely ("marked improvement"), while a far advanced bilateral cavitary lesion might show a much greater absolute improvement, although a much smaller relative change ("moderate" or even "slight" improvement), and still require prolonged hospitalization and surgery. Nevertheless, some such classification is in widespread use. In employing it in the present study, an attempt was made to minimize erroneous conclusions by ensuring ignorance of the regimen used at the time the roentgenogram was interpreted; re-reading at the eight-month point all the four-month films of patients who received eight months of treatment and, again at the 12-month point, films of patients who continued therapy for that time; and having at least two readers for each comparison roentgenogram (9*b*). In any case, it was hoped that any excessive optimism might be equally distributed over both groups of patients. Moderately advanced and far advanced cases were analyzed separately, but the results were combined when the percentages were seen to be almost identical. When the two regimens are compared, a small difference may be noted in the "moderate and marked improvement" category at the four-month point in favor of the twice-weekly regimen. This is no longer seen at the end of eight and twelve months.

It appears that the regimen studied is an effective one and probably about as effective (at least at eight- and twelve-month points) as the streptomycin regimens in more general use. The question arises as to the place of the once-weekly streptomycin regimen in the treatment of tuberculosis. In the opinion of the writers, the regimen would have use chiefly in outpatient therapy for patients who have shown satisfactory improvement with a regimen employing streptomycin at more frequent intervals. In the hospital or sanatorium, the saving of nurses' time may be desirable. Nevertheless, in view of the suggestive figures favoring the twice-weekly regimen at the four-month point, the present writers are reluctant to recommend the use of the once-weekly regimen early in the course of active tuberculosis. With the trend towards longer courses of chemotherapy extending into or even beyond the second year, many patients are being discharged from institutions as having arrested or inactive tuberculosis, with a recommendation to continue chemotherapy on an outpatient basis. It is believed that the savings in time and personnel thus achieved, by cutting the number of visits in two, are worth striving for and make the once-weekly regimen worthy of widespread use. If the patient is working, the saving of his time is also an important factor and may make the difference between his cooperation and the lack thereof.

SUMMARY

Two hundred and nine patients were chosen by random selection to receive one or the other of two regimens consisting of 1 gm. of streptomycin, twice weekly, and 2 gm. of streptomycin, once weekly, each with daily para-aminosalicylic

acid (PAS) or oxytetracycline. Using such criteria as roentgenographic improvement and sputum "conversion," the two regimens were comparably effective at the end of eight and twelve months. At the four-month point, the twice-weekly regimen appeared slightly more effective. It is suggested that the regimen of streptomycin one day a week, with daily PAS, is an effective one for patients who are to continue prolonged chemotherapy upon an outpatient basis after the disease has become arrested.

SUMARIO

La Estreptomicina Una Vez Semanal en el Tratamiento de la Tuberculosis Pulmonar

De dos grupos que recibían regímenes consistentes en 1 gm. de estreptomicina, dos veces semanales, o 2 gm. de estreptomicina, una vez semanal, ambos con ácido para-aminosalicílico (PAS) u oxitetraciclina, diariamente, se tomó al azar a 209 enfermos para estudio. Tomando como pautas la mejoría radiográfica y el viraje del esputo, los dos regímenes resultaron bastante semejantes al cabo de ocho y de doce meses. Al cumplirse cuatro meses, el régimen bisemanal pareció ser un poco más eficaz. Sugiérese que el régimen de estreptomicina, un día a la semana, con PAS diariamente, es muy eficaz para los enfermos que van a continuar una quimioterapia prolongada a base ambulante después de haberse estacionado la enfermedad.

RESUME

Streptomycine une fois par semaine dans la tuberculose pulmonaire

Deux cent-neuf malades ont été répartis au hasard entre deux régimes thérapeutiques. L'un consistant en 1 g. de streptomycine deux fois par semaine et l'autre, 2 g. de streptomycine une fois par semaine avec, dans chaque cas, adjonction d'acide para-aminosalicylique (PAS) ou d'oxytétracycline. Les deux régimes ont donné des résultats absolument semblables au bout de huit et de douze mois, en prenant comme critères l'amélioration des signes radiologiques et la "conversion" des crachats. Au bout de la période de quatre mois, le régime du traitement bi-hebdomadaire paraissait légèrement plus efficace. Les auteurs considèrent que le régime d'administration hebdomadaire avec PAS chaque jour est très satisfaisant pour les cas ambulatoires qui sont destinés à subir un traitement prolongé après stabilisation de l'affection.

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DETECTION OF SMALL NUMBERS OF TUBERCLE BACILLI IN DIAGNOSIS[1]

The Lethal Action of Concentrating Agents

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INTRODUCTION

The necessity for employing chemical means of liquefying tuberculous exudates and of selectively destroying contaminating bacteria has led to an intensive study of the resistance of tubercle bacilli to a wide range of antibacterials. It is by no means certain to what extent the observed resistance of tubercle bacilli to acids, alkalis, and other substances is due to their hydrophobic surface, on the one hand, or to the mechanical protection of centrally placed organisms in large cords or fasicles, on the other.

In recent years, attention has been focused on the fact that a proportion of tubercle bacilli are also killed by the methods adopted to destroy contaminants. Freund and Middlebrook (1) point out that loss of viability and of numbers during digestion may be as high as 90 per cent of the original content. Yegian and Budd (2) have shown that sodium hydroxide treatment, recommended by the American Trudeau Society (3), kills 80 per cent or more of viable tubercle bacilli in a specimen.

The widespread uncertainty concerning the relative merits of the concentration methods in common use is reflected by the number of conflicting reports published in recent years. It is quite impossible to decide from a study of these reports which method is to be preferred. Unquestionably, almost any method will give positive results when the content of tubercle bacilli is high enough to be easily revealed by direct microscopy. As the value of cultural and pathogenicity tests lies chiefly in their usefulness in detecting the small numbers of tubercle bacilli not revealed by direct microscopy, however, the question of selective toxicity becomes extremely important.

Inevitably, the conclusions drawn from studies based on routine bacteriologic examination of specimens have been influenced by a number of important variables. For example, there will be present in any series of specimens an unknown proportion of heavily infected samples which would be positive by any method. This is coupled with lack of knowledge of the initial numbers of viable bacilli in any of the specimens. Moreover, it is impossible to estimate the protective value of clumping and of mucopolysaccharides and other components of the exudate. The interpretation is further complicated by the presence of contaminating organisms in many sputum specimens, notably, gram-positive cocci and *Klebsiella* species, which are able to resist some of the concentration methods. Such a contaminated culture or an animal dying of secondary infection

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[2] Supported by grants from the John Winter Research Fund.

must be included in the negative group regardless of the presence or absence of viable tubercle bacilli. These difficulties are reflected in the remark of Soltys, St. Hill, and Ansell (4) that any comparison of the efficiency of all the various methods of concentrating tubercle bacilli is impossible.

While acknowledging the difficulty of an adequate comparison, the present writers believe that it is not impossible, provided certain conditions can be satisfied. These include:

A knowledge of the number of viable tubercle bacilli originally present in the specimens

The selection of specimens containing small numbers of bacilli not revealed by direct microscopy

Adequate dispersal of the bacilli

Allowances to be made for the possible protective action of the inflammatory products comprising the exudate.

The present paper deals with attempts to apply the above conditions to a study of the lethal action of the common concentration methods. Because no method has yet been devised which will permit an accurate count of the viable tubercle bacilli in untreated clinical material, except, e.g., in tuberculous meningitis, it was necessary to work with dispersed pure cultures. Every effort was made to ensure that the results were not affected by the use of H37Rv as a test strain, or by growing these organisms in the presence of Tween 80.[1]

MATERIALS AND METHODS

Pure culture studies were carried out with *Mycobacterium tuberculosis* H37Rv. After eight serial transfers in Tween-albumin fluid medium, a fresh ampule from dried stock was opened (5).

Unless stated otherwise in the text, the concentrating agents have been prepared and used at the strengths and in the proportions described by Soltys, St. Hill, and Ansell (4). Centrifuging was abandoned when possible to eliminate the tendency of acid-fast bacilli to pack into tight clumps which interfered with later dilutions for counting. It was replaced by dilution of the specimen to 1 in 10 in 0.1 per cent albumin water, and this was taken as the first of the dilution series.

Another disadvantage of centrifuging is the loss of viable units in the supernatant fluid. That this loss is appreciable is shown by counting the supernatant fluid from a suspension centrifuged for thirty minutes at 3,500 r.p.m. in an angle centrifuge. In one such experiment, when a suspension containing 3.5×10^6 viable units per ml. was centrifuged, the supernatant fluid contained 0.025×10^6 viable units per ml., i.e., 0.7 per cent of the original number.

In essentials, the concentration methods were as follows:—

Sodium hydroxide: Final concentration 2 per cent; shaken well and incubated for thirty minutes. Neutralization was carried out at this point in some cases; in others, the exposure was prolonged to one hour before neutralizing to cover the period normally devoted to centrifuging.

Trisodium phosphate: ($Na_3PO_4 \cdot 12H_2O$): Final concentration either 11.5 per cent or 7.5 per cent, the former being the routine practice in the Public Health Laboratory of Victoria. After incubation with occasional shaking for eighteen to twenty-four hours at 37°C., the specimen was diluted as above.

[1] Proprietary name of the polyoxyethylene derivative of Sorbitan monooleate, obtainable from the Atlas Powder Company, Wilmington, Delaware.

Sulfuric acid: Final concentration 3 per cent; shaken well and incubated for thirty minutes at 37°C. The specimen was then diluted without prior neutralization.

Oxalic acid: Final concentration 2.5 per cent; treatment as for sulfuric acid.

Jungmann's method (Nassau's modification) (4):

Solution *A*—Ferrous sulfate, 20 gm.; concentrated sulfuric acid, 20 ml.; distilled water, 180 ml.

Solution *B*—Hydrogen peroxide, 1 volume per cent. (According to Anderson, Hughes, and Knox (6), this concentration is only one-tenth that originally recommended by Jungmann and Gruschka.)

To 5 ml. of specimen were added 3 ml. each of solutions *A* and *B*. This was shaken well, and after ten to fifteen minutes at room temperature plus a further fifteen minutes to allow for centrifuging time, the specimen was diluted for counting.

The media used, oleic-acid–albumin–agar and a modified Löwenstein medium, the counting methods, and animal techniques have been described in the previous papers of this series (5, 7, 8).

When pure cultures were used for quantitative tests, the following practice was adopted. Ten- to twelve-day cultures in liquid Tween-albumin medium were further dispersed with a finely drawn Pasteur pipette, using the inoculation cabinet previously described (5). Following light centrifuging to remove any remaining clumps, the supernatant suspension was standardized in an Evelyn photoelectric colorimeter to a constant reading. This standardized suspension was centrifuged, and the deposit was resuspended to volume in 0.1 per cent albumin water to dilute out the Tween. Samples were then taken and subjected to various treatments or counted to determine the initial numbers. In some experiments, cultures prepared in this fashion were added to nontuberculous sputum.

In experiments in which tuberculous sputum was used, specimens containing approximately 10 organisms per field were selected from clinical material and serially diluted to provide samples containing small numbers of tubercle bacilli.

RESULTS

The Suitability of Washed Cultures Grown in Tween-Albumin Medium

Kirby and Dubos (9) demonstrated that Tween 80 potentiated the action of penicillin on tubercle bacilli, and it appeared necessary to obtain evidence that cultures grown in this medium and subsequently washed were not likely to be abnormally susceptible to concentrating agents. The view that residual Tween 80 in washed cultures grown in Tween-albumin medium does not alter the resistance of tubercle bacilli to the host defenses has been expressed previously (5). The assumption was that the important factor in potentiation is the wetting, not the dispersing action of Tween and, therefore, that its removal by washing was all that was necessary to correct this effect.

The following experiment was designed to determine whether washed, Tween-cultured organisms behave similarly in the presence of penicillin to organisms which have been grown in a medium free from Tween.

From a twenty-one-day-old culture on Löwenstein medium, H37Rv was inoculated into Tween-albumin fluid medium and oleic-acid–albumin fluid medium. To the latter were added a few sterile glass beads, and the cultures were incubated at 37°C. with daily shaking to promote dispersed growth. After twelve days both cultures were lightly centrifuged to remove clumps, and the slightly turbid supernatant fluid was collected and standardized to the same opacity. These suspensions were

TABLE 1

REMOVAL OF POTENTIATING ACTION OF TWEEN 80 BY WASHING CULTURES OF M. TUBERCULOSIS

PENICILLIN UNITS PER ML. OF MEDIUM	PERCENTAGE GROWTH		
	Tween*	Washed Tween*	No Tween†
0	100	100	100
5	95	100	98
10	75	98	100
25	64	100	86
50	18	85	90
100	9	90	93
250	2	75	50
500	0.06	42	38
1,000	0.0018	2.4	1.7

Counts at four weeks

* = Organisms grown in Tween-albumin medium

† = Organisms grown in oleic-acid-albumin medium

Initial number of viable organisms = 3.5×10^6 per ml.

then centrifuged in 5 ml. quantities, and the deposits were resuspended and diluted for counting purposes as below.

1. Tween culture taken up and diluted for counting in Tween-albumin medium
2. Tween culture taken up and diluted for counting in albumin water
3. Oleic-acid–albumin culture taken up and diluted for counting in albumin water

The serial dilutions in each case were spotted in quadruplicate onto oleic-acid–albumin–agar plates containing concentrations of crystalline K penicillin ranging from 0 to 1,000 units per ml. The results after four weeks' incubation are shown as percentage of growth for each concentration of penicillin compared with the control plate containing no penicillin (table 1).

These results on solid medium confirm the observations of Kirby and Dubos (9) in liquid medium. The unwashed organisms (diluted in Tween medium) showed greater susceptibility to the action of penicillin, commencing at 10 units and rising steeply with increasing concentration. It will be seen that one washing was sufficient to remove the potentiating action of Tween, as the resistance of the washed organisms was not significantly different from that of organisms not exposed to Tween during growth. It is concluded that the increased susceptibility to penicillin of dispersed cultures of tubercle bacilli is demonstrable if more than a minimum concentration of Tween is present on the bacterial cell. This concentration is not present after one washing and subsequent plating onto solid medium. It is present if a Tween culture is plated directly. As the degree of dispersal was more or less equivalent in the standardized suspensions used, the inference is that Tween acts by wetting the cell surface rather than by removing the mechanical protection afforded by clumping. This result appeared to justify the use of washed, Tween-dispersed cultures in the present experiments.

The Suitability of H37Rv as a Test Strain

This strain was obviously the most suitable for the purpose of these studies because of its well-known behavior on artificial media and uniformly rapid growth. However, before its reaction to different concentrating agents could be used as an indication of the probable reaction of strains encountered in tuberculous exudates, it was necessary to compare it with freshly isolated strains from clinical cases. Sodium hydroxide treatment was chosen for the test.

Four freshly isolated strains and H37Rv were subcultured from Löwenstein medium into Tween-albumin medium and incubated at 37°C. for ten days. The degree of growth varied a good deal, as usually occurs, but all showed sufficiently dispersed growth for the purpose. Each culture was prepared as above and when suspended in albumin water was divided into two equal portions. To one was added an equal volume of 4 per cent sodium hydroxide and to the other an equal volume of albumin water. After thirty minutes at 37°C., the treated specimens were neutralized and an equivalent volume of albumin water was added to the controls. Viable counts were then made in the usual manner, and the results at four weeks are shown in table 2.

The results are expressed in terms of percentage kill and also as a ratio of killed to surviving organisms. The reason for the latter, which gives a clearer impression of the differences between concentrating agents which caused a very high death rate, will be seen in later tables.

The results under these conditions showed an unexpectedly high rate of killing with all of the strains and, although the H37Rv strain appeared to be the most sensitive to sodium hydroxide, the reaction of the other four strains was by no means uniform. It appeared reasonable, therefore, to employ H37Rv as the test strain.

TABLE 2

RESISTANCE TO 2 PER CENT SODIUM HYDROXIDE OF M. TUBERCULOSIS H37Rv AND OF FOUR FRESHLY ISOLATED STRAINS

STRAIN	VIABLE NUMBERS PER ML.		PERCENTAGE KILL	RATIO KILLED: LIVING
	Initial	Surviving Sodium Hydroxide*		
H37Rv	28×10^6	0.4×10^6	98.5	70:1
Foster	5×10^6	0.3×10^6	94.0	16:1
Dodd	3×10^6	0.08×10^6	97.3	37:1
McLean	56×10^6	1.25×10^6	97.7	44:1
Marshall	10×10^6	1.0×10^6	90.0	10:1

Counts at four weeks on Löwenstein medium.

* = Treatment: equal volume of 4 per cent sodium hydroxide, 30 minutes at 37°C. Neutralized with hydrochloric acid, using Brom thymol blue indicator.

The Lethal Action of Concentrating Agents on Dispersed Cultures of H37Rv in Albumin Water

A fourteen-day culture of *Mycobacterium tuberculosis* (H37Rv) was standardized, washed, resuspended in 0.1 per cent albumin water, and divided into 1 ml. quantities. To each was added the appropriate quantity of either albumin water (control) or one of the six concentrating agents selected. At the termination of treatment, each specimen was made up to 10 ml. with albumin water and this was taken as 10^{-1} for the dilution series. Counts were made in quadruplicate on oleic-acid–albumin–agar. The results, which are representative of several similar experiments, are shown in table 3.

All of the concentrating agents were observed to retard growth; some more than others. At thirteen days the control series showed visible growth up to and including the highest dilution finally yielding countable colonies. At this stage, sulfuric acid, oxalic acid, and Jungmann's treatment showed no growth, sodium hydroxide showed moderate growth, and trisodium phosphate was intermediate between the latter and the controls, with no growth in the 10^{-4} and 10^{-5} dilutions which later proved countable. In the ensuing two weeks, countable colonies were present in all cases and the numbers remained constant thereafter. However, the inhibitory effect of sulfuric acid, oxalic acid, and Jungmann's solution was still evident in the small size of these colonies, compared with the controls. The inhibitory effect was least noticeable with sodium hydroxide and trisodium phosphate, and there was little to choose between these two methods in terms of final counts, although both killed more than 80 per cent of the organisms.

No attempt is made to reconcile the figures for sodium hydroxide in this experiment with the data in table 2; and, indeed, in a dozen different experiments during three years, the death rate has ranged from 98.5 per cent to 74 per cent. It is assumed that variations in the sodium hydroxide solutions, cultures, and batches of media used for counting may be partly responsible. As these conditions were constant for any one experiment, the results are considered to be

TABLE 3

LETHAL ACTION OF CONCENTRATING AGENTS ON DISPERSED CULTURES OF H37Rv IN ALBUMIN WATER

TREATMENT				VIABLE UNITS PER ML. $\times 10^9$	PERCENTAGE KILL	RATIO KILLED: LIVING
Concentrating Agent	Final Concentration	Time	Temperature			
	per cent					
Nil (albumin water)	—	30 minutes	37°C.	180.0	0	0
Sodium hydroxide	2.0	30 minutes	37°C.	23.0	87.2	7:1
Trisodium phosphate	11.5	24 hours	37°C.	22.5	87.5	7:1
Sulfuric acid	3.0	30 minutes	37°C.	3.5	98.1	50:1
Oxalic acid	2.5	30 minutes	37°C.	1.2	99.3	150:1
Jungmann	54.5	30 minutes	21°C.	0.054	>99.9	3,300:1

Counts at four weeks.

comparable. However, if the time of exposure to sodium hydroxide was increased from thirty minutes to one hour, the percentage kill was greatly increased.

Pure Cultures Added to Nontuberculous Sputum

For this study a specimen of sputum was selected from a nontuberculous person suffering from chronic bronchitis. It was rich in mucoprotein and showed a large number of polymorphonuclear leukocytes and gram-negative bacilli. These were *Klebsiella pneumoniae*, which proved to be a stubborn contaminant.

Two methods were used and for convenience they will be reported together. In the first instance, the sputum was homogenized in a Waring Blendor for three minutes. The culture, prepared as before, was divided into 0.1 ml. amounts; to these 0.9 ml. of sputum was added; and to the control, 0.9 ml. of albumin water. The mixtures were shaken and the subsequent treatment was as described before, the treated specimens then being diluted and counted.

In the second method, culture was added in bulk to the homogenized sputum and mixed for five seconds in the blender. Tenfold serial dilutions were made in 25 per cent sputum, and 1 ml. of each dilution was then treated separately with the appropriate concentrating agent. The treated specimens were either diluted or neutralized, then centrifuged at 3,500 r.p.m. for thirty minutes, and the supernatant fluid was discarded. The deposits were taken up in 1 ml. albumin water and, when thoroughly mixed, four drops from each dilution were counted on oleic-acid–albumin medium. This method was designed to eliminate any counting error resulting from clumping during treatment. The results are set out in table 4.

The presence of sputum does not appear to have exerted any marked influence on the lethal action of the agents used (*see* table 3). In general, this experiment confirms the previous observations with H37Rv in albumin water and also those

TABLE 4

LETHAL ACTION OF CONCENTRATING AGENTS ON H37Rv ADDED TO SPUTUM

TREATMENT		SPUTUM DILUTED AFTER TREATMENT			SPUTUM DILUTED BEFORE TREATMENT		
Concentrating Agent	Final Concentration	Viable Units $\times 10^5$	Percentage Kill	Ratio Killed: Living	Viable Units $\times 10^4$	Percentage Kill	Ratio Killed: Living
	per cent						
Nil (culture)	—	11	0	0	72	0	0
Sodium hydroxide (uninoculated sputum)	2.0	0	—	—	0	—	—
Sodium hydroxide	2.0	2	81.8	4.5:1	11	84.7	5.5:1
Trisodium phosphate	11.5	C	—	—	C	—	—
Oxalic acid	2.5	0.7	93.6	15:1	1.4	98.1	50:1
Sulfuric acid	3.0	0	100.0	—	0.3	99.6	240:1
Jungmann	54.5	0	100.0	—	0.06	>99.9	1,200:1

Counts at three and five weeks. C = contaminated; *K. pneumoniae* present in a concentration of 90×10^6 per ml. after trisodium phosphate treatment.

of Yegian and Budd (2) and of Spendlove and his co-workers (10) that sodium hydroxide is not affected by sputum. The apparent destruction of more than one million tubercle bacilli by the sulfuric acid and Jungmann methods may be related to the tendency of these two processes to cause clumping of bacilli. When the possible effects of such clumping were counteracted by diluting the sputum and then treating the diluted samples, some survival occurred. This may be related to the heavier suspension treated and, in any case, neither method compared at all favorably with sodium hydroxide. No conclusion can be drawn for trisodium phosphate from this experiment.

Recovery of Tubercle Bacilli from Treated Tuberculous Sputum by Culture and Animal Inoculation

Another method of assessing the relative merits of concentrating agents is to treat tuberculous sputum and then to determine the highest dilution of the various concentrates capable of infecting animals and of producing growth on artificial media. The results of such an experiment have been recorded in part in a previous paper (8).

A sputum positive for tubercle bacilli of unknown bacillary content was homogenized for five seconds in a Waring Blendor, and 1 ml. samples were treated and then diluted for counting. From the dilutions, equal amounts were taken to inoculate Löwenstein medium, one guinea pig intramuscularly, and two C57 black mice intranasally. The latter animals were kept on a reduced diet from the time of inoculation (5, 8). The mice were killed at three weeks and the guinea pigs at six weeks if palpable adenitis was present; if not, they were left for ten weeks. Cultures were examined at four weeks and at six weeks (table 5).

The results obtained confirm previously observed trends. In this experiment, 2 per cent sodium hydroxide treatment for thirty minutes and 11.5 per cent

TABLE 5

RECOVERY OF TUBERCLE BACILLI FROM TUBERCULOUS SPUTUM, TREATED AND SUBSEQUENTLY DILUTED

TREATMENT		HIGHEST DILUTION POSITIVE BY:		
Concentrating Agent	Final Concentration	Culture (Number of Colonies)	Guinea Pig Intramuscular 10 Weeks	Mice Intranasal 3 Weeks
	per cent			
Sodium hydroxide	2.0	10^{-3} (6)	10^{-4}	10^{-3}
Trisodium phosphate	11.5	10^{-3} (8)	10^{-4}	10^{-4}
Trisodium phosphate	7.5	10^{-3} (10)	10^{-4}	10^{-3}
Oxalic acid	2.5	10^{-3} (3)	10^{-4}	10^{-3}
Sulfuric acid	3.0	* 10^{-1} negative	10^{-1} negative	—†
Jungmann	54.5	* 10^{-1} negative	10^{-1} negative	10^{-1} negative

* = Not tested at full strength, i.e., centrifuged deposit of undiluted concentrate.

† = Mice died within twenty-four hours of intranasal inoculation (0.3 per cent sulfuric acid solution and 0.25 per cent oxalic acid solution alone were lethal to mice by the intranasal route).

trisodium phosphate for twenty-four hours were equally lethal, while 7.5 per cent trisodium phosphate was slightly less lethal. Oxalic acid was more lethal than the above, and the other methods yielded negative results.

DISCUSSION

When the number of tubercle bacilli in a specimen is large, any method of concentrating will yield some survivors. For this reason these studies were based on specimens containing small numbers of tubercle bacilli. Moreover, specimens of this nature constitute a far more important problem in diagnosis. An attempt has been made to arrive at a quantitative assessment of the lethal action of common methods of homogenizing sputum and destroying contaminants for cultural purposes and animal inoculation.

It has been demonstrated that the action of Tween in diminishing the resistance of tubercle bacilli to antimicrobials, as indicated by penicillin susceptibility, is due to its wetting properties rather than to dispersal of protective clumping. This action may be eliminated by simple washing, thus justifying the use of washed dispersed cultures grown in Tween-albumin medium for these experiments.

Whether tubercle bacilli were obtained from washed dispersed cultures and suspended in albumin water or in nontuberculous sputum, or occurred naturally in clinical material, the same lethal trend was observed with the different concentrating agents. Although with all treatments the kill was usually greater than 80 per cent, sodium hydroxide and trisodium phosphate gave similar results and were the least lethal. There appears to be a considerable risk with sulfuric acid and Jungmann's solution that both methods will yield a completely negative result if the numbers of tubercle bacilli present do not greatly exceed 1×10^6 viable organisms. Oxalic acid exerted an effect intermediate between these two groups. In addition, the growth of treated bacilli on artificial media was retarded in comparison with untreated organisms. This effect was least marked with trisodium phosphate and sodium hydroxide.

It has been the experience of the Public Health Laboratory of Victoria that, for gastric contents and for sputum which may be delayed in transit or arrive too late at the laboratory to be included in the daily tests, trisodium phosphate added at the bedside offers certain advantages over sodium hydroxide.

The reflection of these findings on the reliability of cultural and animal studies, especially when a bacteriologic "clearance" is required following successful clinical regression, is so evident as to need no further emphasis. The discovery of less lethal concentration methods is obviously desirable.

In parallel with these studies, a number of other possible methods have been investigated. These include the use of urea, papain, pancreatin, and bacterial enzymes of various types, e.g., *Clostridium sporogenes* and *Streptomyces albus*. Three properties were sought: ability to liquefy all types of sputum; selective toxicity for contaminants compared with acid-fast bacilli; and simplicity of handling for routine use. On one or other of these grounds, all of the above have proved less efficient than either sodium hydroxide or trisodium phosphate.

SUMMARY

Experiments have been carried out to assess the lethal effects on tubercle bacilli of several concentrating methods in general use.

Lethal effects were determined quantitatively on known numbers of organisms suspended in albumin water or in nontuberculous sputum.

Tuberculous sputum was used to confirm the relative toxicity of the concentrating agents.

All of the methods tested killed 80 to 100 per cent of the tubercle bacilli present.

Sodium hydroxide for thirty minutes and trisodium phosphate for eighteen to twenty-four hours were the least lethal of the substances tested.

SUMARIO

El Descubrimiento de Pequeñas Cantidades de Bacilos Tuberculosos en el Diagnóstico: La Acción Letal de los Concentradores

Los experimentos llevados a cabo se proponían justipreciar los efectos letales que ejercen sobre los bacilos tuberculosos las varias técnicas de concentración empleadas generalmente.

Se determinaron cuantitativamente los efectos letales ejercidos sobre cantidades conocidas de microbios suspendidos en agua albuminosa o en esputo no tuberculoso.

Se usó esputo tuberculoso para confirmar la toxicidad relativa de los concentradores.

Todas las técnicas ensayadas mataron de 80 a 100 por ciento de los bacilos tuberculosos que había presentes.

El hidróxido de sodio durante treinta minutos y el fosfato trisódico durante dieciocho a veinticuatro horas fueron los menos letales.

RESUME

La decouverte d'un petit nombre de bacilles tuberculeux en diagnostic: L'action léthale des agents d'homogénéisation

Des expériences ont été effectuées pour évaluer l'action léthale exercée sur le bacille de Koch par un certain nombre de méthodes d'homogénéisation usuelles.

L'action léthale était déterminée quantitativement en prenant pour base un nombre connu de bacilles suspendus dans l'eau albumineuse ou dans le crachat non tuberculeux.

L'expectoration bacillifere était employée pour évaluer la toxicité relative des agents utilisés pour l'homogénéisation.

Dans toutes les méthodes expérimentées, 80 à 100% des bacilles tuberculeux présents étaient tués.

L'hydroxyde de sodium agissant pendant trente minutes et le phosphate trisodique pendant dix-huit à vingt-quatre heures ont donné le taux de léthalité le plus bas.

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A COMPARISON OF LEUKOCYTE LYSIS WITH CERTAIN OTHER IMMUNOLOGIC PHENOMENA DEMONSTRABLE IN SERA OF TUBERCULOUS RABBITS[1,2]

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INTRODUCTION

Immunization of rabbits by appropriate techniques with purified proteins (ovalbumin, bovine gamma globulin) results in formation of thermostable, nonprecipitating antibody capable of lysing normal rabbit polymorphonuclear leukocytes in the presence of homologous antigen (1). A thermolabile component in serum from tuberculous mice, guinea pigs, and humans induces lysis of both polymorphonuclear cells and lymphocytes (2, 3, 4). While considerable time has been devoted to investigation of tuberculous antibodies lysing erythrocytes in the presence of antigen and complement (*see* (5) for review of this field), little attention has been given to extending the observations on leukocyte lysis as a serologic activity of tuberculous sera. It seemed advisable, therefore, to investigate lysis of leukocytes as observed in the blood of rabbits sensitive to tuberculin and to compare it with (*1*) the specific lysis found in other tuberculous animals and in protein-sensitized rabbits, and (*2*) other serologic properties of tuberculous blood. Observations are also reported relating this *in vitro* lysis to the effects of intravenous tuberculin injection on the blood picture of sensitized rabbits.

METHODS

Inoculations and bleeding: Mature, albino, female rabbits of a mixed strain, weighing 2.5 to 3.0 kg., were inoculated by the following techniques. Some were given 2 mg. doses (semidry weight) of BCG[4] intradermally in one or more foot pads, with total doses varying between 2 and 16 mg. Others were inoculated in the foot pads with heat-killed human-type tubercle bacilli[5] in Bayol F (4 mg. per ml.), with total doses of 0.4 to 1.6 mg. A third group received intravenous injections twice weekly for six weeks of 2 mg. doses of the same heat-killed organisms suspended in 1.0 ml. of saline. All were bled from the heart on the days indicated in the tables. If the blood was to be used in a lysis test, the syringe was moistened with heparin (Liquaemin Sodium, Organon, containing 10 mg. of heparin per ml.) and the blood was mixed with the aid of an air bubble immediately after being drawn. Otherwise, serum was obtained and stored at −15°C.

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[4] The BCG was very kindly supplied us by Dr. Konrad Birkhaug of the New York State Department of Health.

[5] Dr. Jules Freund of the Public Health Research Institute of the City of New York, Inc., was good enough to provide the tubercle bacilli (Jamaica 22 strain) used in this work.

Tuberculin: The Massachusetts State Antitoxin and Vaccine Laboratories' Old Tuberculin (OT) and Lederle's special OT, lot number 2725-33,[6] both four times standard strength, were used in all skin tests and in the earlier lysis studies. Fresh dilutions, based on the standard, were prepared weekly. Dilutions of 1:5 and 1:20 were used in most lysis tests, 1:10 in a few others; 1:100 consistently failed to cause lysis. Purified protein derivative (PPD) (Parke-Davis & Co.) was used in concentrations of 5 and 50 γ per ml. in saline in all later lysis tests. While the PPD had no effect on normal blood, both samples of OT became lytic for normal leukocytes after long standing at −4°C. No lysis results obtained after this nonspecific lytic activity developed are included in the tables.

Leukocyte lysis tests: The procedure employed in estimating lysis was identical with that previously described (1), involving the use of siliconed tubes and the carrying out of all stages of the procedure in duplicate. Tuberculin dilution or saline (0.1 ml.) was incubated with 0.4 ml. of test blood or with 0.2 ml. of test serum plus 0.2 ml. of fresh, normal rabbit blood. The decrement $\triangle$, as before, represents the difference between the average percentage fall in leukocyte count in the tubes containing tuberculin and that in the saline tubes. Differences of less than 10 per cent are of dubious significance and are considered negative. The reliability of the values obtained in this manner is indicated in the various tables (*see* particularly table 5). During many of the lysis tests, smears were prepared for differential counts and stained with Wright's stain. More than 200 cells were counted in each instance.

Other serologic methods: The erythrocyte agglutination tests followed in most details the technique of Smith and Scott (6) and need not be described further. For these, the Lederle OT preparation was used. The sera, after inactivation and absorption, were also used for precipitin and complement fixation tests with the Lederle tuberculin. For the precipitins, sera diluted 1:2 were mixed with equal amounts of tuberculin diluted 1:10, 100, and 1,000 and were incubated for one hour at 37°C. and for forty-eight hours at 4°C. They were graded as one-plus when precipitate appeared in one tube, two-plus in two tubes, and three-plus in all three tubes. No precipitate was observed with antigen diluted to 10,000. Complement fixation was performed with the usual Wassermann technique, with tuberculin 1:100 as antigen, with initial serum dilutions of 10, 20, 40, and 80, and with complement standardized photometrically at six 50 per cent hemolytic units. Titers are reported as the serum dilution, before addition of sensitized cells, in the last tube showing definite inhibition of hemolysis.

RESULTS

Leukocyte lysis in fresh blood: A preliminary survey was carried out to determine whether lysis of leukocytes occurred after addition of tuberculin to fresh, heparinized blood of rabbits tuberculin-sensitized by different procedures. Illustrative protocols of two positive tests are presented in table 1. Of interest is the observation that lysis was more marked after six hours of incubation than after one hour. Almost all tests in which counts were performed at various intervals after the addition of tuberculin to the blood demonstrated the same relatively delayed fall in total count (figure 1). The leukocyte lysis observed here thus differs from that found with antisera against egg albumin or bovine gamma globulin, in which lysis occurs more promptly. The difference may be attributed to the fact that lymphocytes are lysed as well as polymorphonuclear cells (table 2), although to a lesser degree. Lymphocytes are not affected in lysis by protein antisera (1). From table 2, it appears that destruction of lymphocytes occurs mostly after the first hour. However, in stained smears examined at one hour (figure 2), many obviously damaged cells of both major types could be found,

[6] Obtained through the courtesy of Dr. H. D. Piersma of the Lederle Laboratories.

TABLE 1

PROTOCOLS OF LYSIS EXPERIMENTS WITH WHOLE BLOOD AND TUBERCULIN*

TEST BLOOD	ANTIGEN	0 MINUTES	1 HOUR			6 HOURS		
		Total Counts	Total Counts	Average Per Cent Change	Δ	Total Counts	Average Per Cent Change	Δ
					per cent			*per cent*
11	Saline	335	303	−5.8		287	−12.6	
		314	309			280		
	OT 1:20	335	232	−16.3	−10.5	232	−23.1	−10.5
		279	281			240		
	OT 1:5	297	278	−7.9	−2.1	211	−32.0	−19.4
		309	280			201		
17	Saline	487	466	−2.7		473	−6.5	
		408	406			364		
	OT 1:20	488	437	−3.6	−0.9	395	−21.0	−14.5
		394	412			300		
	OT 1:5	433	371	−11.5	−8.8	293	−39.6	−33.1
		473	431			255		

* OT of Massachusetts State Laboratories.

TABLE 2

LYSIS OF DIFFERENT CELL TYPES BY TUBERCULIN

TEST BLOOD	OT* CONCENTRATION	TIME	PERCENTAGE CHANGE		
			Total Count	Total Polymorphonuclears†	Total Lymphocytes†
		hours			
11	1:20	1	−16.3	−33.8	−2.9
		6	−23.1	−40.0	−11.0
	1:5	1	−7.9	−16.4	0.0
		6	−32.0	−44.5	−22.8
14	1:5	4	−14.9	−28.5	−6.9
17	1:20	1	−3.6	+2.6	−8.6
		6	−21.0	−35.5	−8.9
	1:5	1	−11.5	−15.3	−5.6
		6	−39.6	−50.9	−30.8

* OT of Massachusetts State Laboratories.

† Other types of cells were counted but are disregarded here.

although these same cells were still counted as normal in the total leukocyte counts. Such cells were vacuolated and adherent to masses of amorphous material resembling degenerating clumps of platelets. In the case of rabbit No. 11, for example (tables 1 and 2, figure 2), 78 per cent of the polymorphonuclears remaining at one hour in the tube containing 1:20 tuberculin were vacuolated or otherwise damaged.

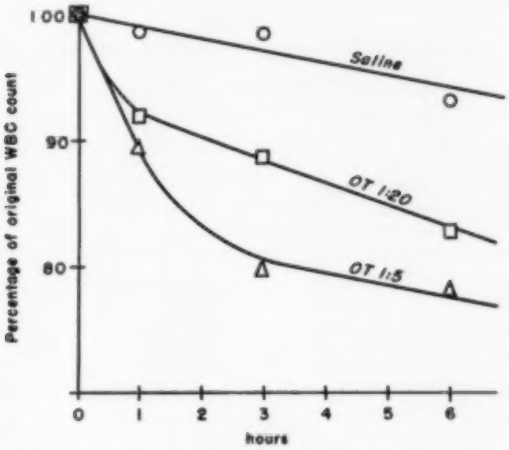

FIG. 1. Change of total leukocyte count with time in tuberculous bloods exposed to saline — ○; OT 1:20 — □; and OT 1:5 — △. Points represent average figures for 7 positive animals.

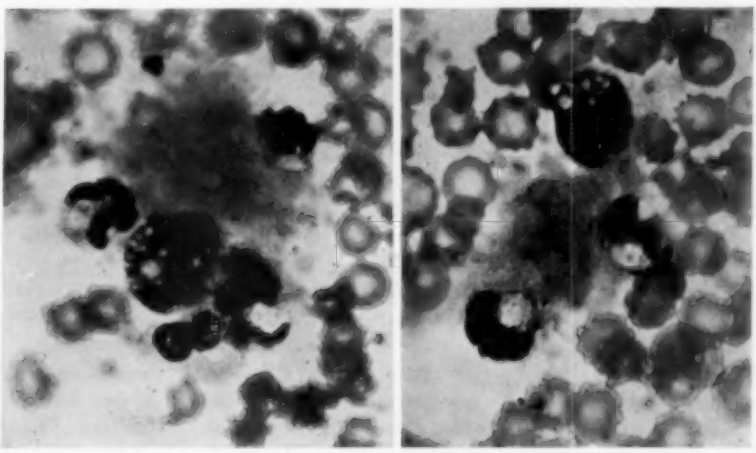

FIG. 2. Rabbit No. 11. Fresh blood plus tuberculin 1:20. Smears at one hour (×1,000, Wright's stain). Damaged polymorphonuclear cells and lymphocytes adherent to masses of amorphous, basophilic material (fused platelets?).

In table 3 the results of skin testing tuberculin-sensitive rabbits with OT are compared with the results of lysis tests on fresh blood of these animals. Between twenty and fifty-eight days following inoculation, no relation is seen between the degree of skin reactivity to tuberculin and the ability to give a positive lysis test *in vitro*. Approximately one-third of the animals tested showed clear-

TABLE 3

COMPARISON OF LEUKOCYTE LYSIS WITH CUTANEOUS SENSITIVITY TO TUBERCULIN

RABBIT	METHOD OF SENSITIZATION	DAY OF SKIN TEST*	INDURATION AT 48 HOURS	DAY OF LYSIS TEST*	Δ
	BCG		*cm. mm.*		*per cent*
1	2 mg. intradermally	41	162	57	−11.5
2	2 mg. intradermally	41	392	58	Neg.
3	2 mg. intradermally	41	450	43	Neg.
4	8 mg. intradermally	23	900	—	—
5	8 mg. intradermally	41	450	55	Neg.
6	16 mg. intradermally	23	972	—	—
7	16 mg. intradermally	23	338	—	—
	Tubercle Bacilli in Oil				
11	0.4 mg. intradermally	20	225	29	−19.4
12	0.4 mg. intradermally	20	169	29	Neg.
13	0.4 mg. intradermally	20	64	37	Neg.
14	0.4 mg. intradermally	20	72	36	−21.1
16	0.8 mg. intradermally	20	169	—	—
17	0.8 mg. intradermally	20	1,200	27	−33.1
18	0.8 mg. intradermally	20	72	37	−23.4
19	0.8 mg. intradermally	20	648	—	—
51	1.6 mg. intradermally	26	675	26	Neg.
52	1.6 mg. intradermally	26	200	26	−32.9
53	1.6 mg. intradermally	26	50	26	−22.1
54	1.6 mg. intradermally	26	100	26	−9.6
55	1.6 mg. intradermally	26	432	26	−8.3

* All cutaneous tests and counts done with OT of Massachusetts State Laboratories. Skin tests with OT 1:100. Lysis tests with 1:20 and 1:5; Nos. 51 to 55 tested with OT 1:10.

cut lysis in tests lasting two to six hours. In the table certain animals are included whose sera were later studied for the leukocyte lytic property, although no test was carried out with fresh blood.

The course of leukocyte lytic capacity as measured in fresh bloods of rabbits in the group receiving prolonged intravenous immunization with heat-killed tubercle bacilli is illustrated in table 4. Significant falls in leukocyte count are shown in heavy type. The same data, averaged for the 5 animals, are shown graphically in figure 3. In a few instances (Nos. 22 and 24 on the fifteenth to seventeenth days, No. 21 on the twenty-second to twenty-fifth days), the fall in the saline control was such as to prevent adequate evaluation of leukocyte changes in the tubes containing tuberculin. It appears, nonetheless, that lysis attributable to the added tuberculin occurred in the blood of at least 2 of these 5 animals. The lytic property seems to reach a maximum at approximately two weeks, then slowly to wane. This course is comparable to the early rise and subsequent decrease of leukocyte lytic power in the blood of rabbits which receive repeated protein injections (1). Table 4 provides some criterion of the validity of data presented in the present report. Of 22 determinations, only 2 showed a fall in leukocyte count in the saline control significantly greater than the fall in tubes containing tuberculin.

TABLE 4

LEUKOCYTE LYSIS DETERMINATIONS DURING INTRAVENOUS IMMUNIZATION WITH TUBERCLE BACILLI*

DAY	ANTIGEN	SERUM NUMBER 20		SERUM NUMBER 21		SERUM NUMBER 22		SERUM NUMBER 23		SERUM NUMBER 24	
		Per Cent Fall	Δ	Per Cent Fall	Δ	Per Cent Fall	Δ	Per Cent Fall	Δ	Per Cent Fall	Δ
8	Saline	+1.3		−7.7		−18.9					
	OT 1:20	−11.1	**−12.4**	−12.0	−4.3	−13.6	+5.3	—	—	—	—
	1:5	−6.2	−7.4	−15.3	−7.6	−26.3	−7.4				
15–17	Saline	−5.6		−13.3		−21.5		−13.3		−22.4	
	OT 1:20	−29.8	**−24.2**	−8.9	+4.4	−30.7	−9.2	−19.2	−6.5	−25.2	−2.8
	1:5	−34.8	**−29.2**	−28.5	**−15.2**	−30.8	−9.3	−12.7	+0.6	−22.6	−0.2
22–25	Saline	−13.3		−22.9		−10.8		+4.1		−8.6	
	OT 1:20	−20.8	−7.5	−28.3	−5.4	−1.8	+9.0	−5.6	−9.7	−10.0	−1.4
	1:5	−26.2	**−12.9**	−25.9	−3.0	−19.5	−8.7	−18.5	**−22.6**	−0.1	+8.5
29–31	Saline	−2.5		+0.9		−0.2		−14.8		−13.3	
	OT 1:20	−1.2	+1.3	−9.8	**−10.7**	−6.5	−6.3	−13.0	+1.8	−8.7	+4.6
	1:5	−6.5	−4.0	−16.2	**−17.1**	−29.1	**−28.9**	−3.3	+11.5	−17.4	−4.1
42–44	Saline			−1.8		−15.3		−14.2		−2.7	
	OT 1:20	—	—	+1.9	+3.7	−1.0	+14.3	−16.3	−2.1	+0.4	+3.1
	1:5			−17.4	**−15.6**	−11.4	+3.9	−28.4	**−14.2**	−10.0	−7.3

* All determinations carried out with Lederle's OT. Duration of experiment two hours. Significant decrements given in heavy type.

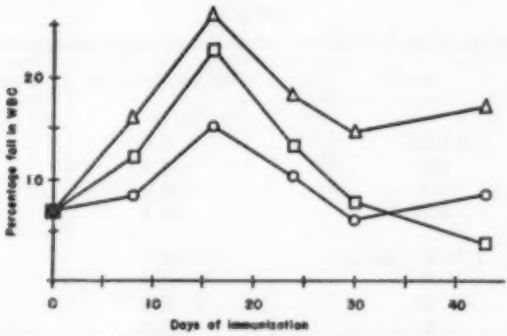

FIG. 3. Variations of leukocyte lytic activity during intravenous immunization with tubercle bacilli. Points represent averages of the figures in table 4, i.e., two-hour determinations with saline — ○; OT 1:20 — □; and OT 1:5 — △.

The induction of lysis by serum and its relation to other demonstrable antibodies: In table 5 are shown replicate lysis determinations using PPD, alone and with one of the test sera, together with a series of normal bloods. While there is considerable variation, it is clear that falls in leukocyte count attributed to the added tuberculin cannot be due to chance. The occasional spontaneous lysis of cells is illustrated by the data obtained with normal blood on May 20, 1953.

TABLE 5

REPLICATE LYSIS DETERMINATIONS WITH NORMAL BLOOD WITHOUT AND WITH LYSING ANTISERUM

DATE	NORMAL BLOOD			DATE	NORMAL BLOOD PLUS SERUM NUMBER 23		
	Change of Leukocytes with:				Change of Leukocytes with:		
	Saline	PPD 5γ per ml.	PPD 50γ per ml.		Saline	PPD 5γ per ml.	PPD 50γ per ml.
	per cent	*per cent*	*per cent*		*per cent*	*per cent*	*per cent*
February 3, 1953	−1.7	−17.5	+7.6	March 20, 1953	−4.8	−23.0	−16.3
	−20.1	+1.2	−14.3	March 23, 1953	−5.5	−19.6	−7.4
February 5, 1953	−4.0	−5.9	−2.1	March 25, 1953	−7.7	−1.5	−7.8
	−4.8	−10.3	−2.4	March 27, 1953	−6.3	−16.1	−21.4
February 6, 1953	−9.9	−1.3	−5.1	March 30, 1953	−7.7	−17.3	−20.5
	−7.8	−0.4	−6.5	April 1, 1953	−5.0	−11.3	−28.1
February 12, 1953	−5.7	−11.6	−4.9	April 3, 1953	−2.3	−14.0	−14.4
	−14.2	−2.0	+1.0				
April 27, 1953	−11.6	−2.9	+1.0				
May 18, 1953	−2.9	−2.5	−6.3				
May 20, 1953	−21.6	−22.3	−31.2				
May 25, 1953	+0.8	−3.2	+0.5				
Averages.....	−8.6	−6.6	−5.2		−5.6	−14.7	−16.6
Average decrements						−9.1	−11.0
t						3.14	3.66
P						0.02	0.01

TABLE 6

EFFECT OF HEAT ON LEUKOCYTE LYTIC POWER OF TUBERCULOUS SERA*

SERUM SAMPLE	ANTIGEN	Δ WITH UNHEATED SERUM	Δ WITH HEATED SERUM
		per cent	*per cent*
3	OT 1:20	−8.0	+5.6
	1:5	−11.2	+5.7
14	1:20	−10.7	+2.8
19	1:20	−21.1	−13.2
1	PPD 5 γ per ml.	−12.0	−13.6
	50	−10.8	−3.4
2	50	−8.3	−17.2
5	5	−18.6	−29.7
7	5	−11.9	+9.0
	50	−13.3	+4.3
21	PPD 5 γ per ml.	−3.5	−23.5
	50	−13.1	−28.0
22	5	−6.0	−11.7
	50	−12.5	−12.6
23	5	−23.0	−33.4
	50	−16.3	−5.3

* All sera were heated at 57°C. for four hours. Many of the heated and unheated pairs were tested simultaneously with a single sample of fresh normal blood.

The failure of some normal bloods to show lysis in the presence of active serum and antigen is shown by the findings on March 25, 1953, with serum No. 23.

The active lytic component of sera from immunized rabbits appears in general to be heat-stable (table 6).

In table 7 are tabulated leukocyte lysis determinations together with the

TABLE 7

COMPARISON OF LEUKOCYTE LYSIS WITH OTHER PROPERTIES OF TUBERCULOUS SERA

RABBIT	DAY OF BLEEDING	LEUKOCYTE CHANGE*			SHEEP CELL AGGLUTINATION TITER	PRECIPITIN	COMPLEMENT FIXATION TITER
		Saline	PPD 5 γ per ml.	PPD 50 γ per ml.			
		per cent	*per cent*	*per cent*			
1	45	−6.5	**−18.5**	−17.3	24	0	120
	51	−5.5	**−30.1**	**−20.3**	8	+	60
2	45	−11.3	**−23.6**	−19.6	>72	0	60
	51	−9.8	−10.7	−9.8	>72	0	60
4	28	−9.9	−10.8	−8.6	0	0	60
5	45	−9.8	**−28.4**	+2.2	72	0	60
	51	−16.2	−24.6	−12.8	72	0	60
6	28	−5.3	−13.3	−12.9	8	0	120
7	28	−5.6	**−17.5**	**−18.9**	72	0	60
11	24	+3.7	+1.7	−5.9	8	+	60
12	24	+22.0	−4.2	−11.2	8	0	60
13	24	−4.5	−0.5	−2.4	72	+++	30
	31	−0.4	**−26.1**	**−23.7**	72	+++	60
14	24	−4.3	−7.5	−6.2	72	0	240
	31	−6.5	−12.3	—	24	0	120
16	20	−5.1	−2.8	**−20.4**	>72	0	60
17	24	−4.9	**−16.3**	−11.2	72	0	60
18	24	−0.3	−3.9	−0.9	24	0	120
	31	−4.4	−5.2	−6.2	24	0	120
21	44	−2.3	−5.8	**−15.4**	>72	0	120
22	44	−3.7	−9.7	**−16.2**	72	0	240
23	44	−4.8	**−23.0**	**−16.3**	>72	0	120
24	44	−1.2	**−20.8**	**−26.4**	>72	0	240
69	20	−17.9	−4.0	−7.2	8	0	60
70	20	−21.6	−5.8	−9.5	8	+++	120
71	21	−26.2	−18.0	−12.2	0	++	0
72	21	−10.9	−18.5	**−23.1**	0	+++	0
74	21	−4.1	−6.5	−10.1	8	+	60
75	20	−7.1	−17.9	−17.9	0	++	120
76	20	−1.3	−11.2	**−13.2**	24	++	0
77	21	−2.4	**−19.5**	**−20.6**	8	0	0
78	21	−5.6	−7.0	−10.3	0	++	120
79	21	−0.6	**−12.9**	**−12.4**	8	+	60
80	21	−14.8	−12.3	**−28.3**	8	0	120

* Falls of 12 per cent or more are given in heavy type.

erythrocyte agglutination, precipitin, and complement fixation findings for the sera of rabbits in the three groups already described and in a fourth group (Nos. 69–80). The last-named animals had been inoculated intradermally with 0.6 mg. of heat-killed tubercle bacilli in Bayol F and bled at twenty-one days. The four types of serologic activity were not parallel. However, of 17 sera giving leukocyte decrements greater than approximately 12 per cent (shown in heavy type), 10 produced erythrocyte agglutination at titers of 72 or more, while, of the 17 negative or dubiously positive sera, only 4 showed equal titers. As this difference is statistically significant ($P < 0.05$), there appears to be some correlation of the two serologic properties. The sera of the 4 rabbits immunized with repeated intravenous injections of tubercle bacilli were quite active in both types of test. Of the 34 leukocyte lysis determinations, only 3 showed falls in the saline tubes significantly greater than those in tubes which contained PPD.

The effect of injected tuberculin on leukocyte counts: It has been suggested (7) that the fall in lymphocytes following intravenous tuberculin administration in tuberculin-sensitive rabbits depends on lysis of the type investigated by Favour and associates (2, 3, 4) and in the present report. Therefore, 10 of the rabbits in the first two groups were given intravenous injections of OT (Massachusetts State) in amounts between 10 and 400 mg. Total and differential leukocyte counts were done at various intervals up to forty-eight hours. A sample of blood obtained immediately before the tuberculin injection was used for the usual type of leukocyte lysis study, followed to six hours. In addition, a blood sample taken from an ear vein immediately after the intravenous dose of OT was rotated in a siliconed tube at 37°C. for several hours while repeated counts were made. All counts and differentials were done in duplicate. In the rabbits themselves, a fall in lymphocytes, usually maximal at six hours and corresponding to the rise in temperature observed, occurred as reported (7). The observed fall varied between 25.8 and 86.8 per cent of the total number of lymphocytes, with an average fall of 67.0 per cent. The temperature rose between 2.0° and 6.1°C., with an average rise of 3.0°C. Polymorphonuclears disappeared almost completely from the bloodstream in the first few minutes, then reappeared and rose, sometimes considerably above the control level; but by six hours these cells were usually back to normal.

TABLE 8

IMMEDIATE LEUKOCYTE CHANGES IN RABBIT NUMBER 1 AFTER INTRAVENOUS INJECTION OF 40 MG. OF OT

TIME	TOTAL LEUKOCYTE COUNT	POLYMORPHONUCLEARS	LYMPHOCYTES
−60 seconds	5,300	2,200	3,100
+30 seconds	4,400	2,400	1,900
+60 seconds	3,300	1,300	2,000
5 minutes	1,500	300	1,200
15 minutes	4,200	1,400	2,800
1 hour	9,900	4,200	5,800
6 hours	5,800	3,500	2,300

TABLE 9

COMPARISON OF LEUKOCYTE COUNT CHANGES IN VIVO, IN VITRO, AND IN USUAL LYSIS TEST

Rabbit	5			17			Control		
Mg. of OT injected	400			40			40		
Time in hours	0	1	6	0	1	6	0	1	6
Rectal temperature	103.2°	105.8°	105.2°	102.4°	104.8°	105.4°	103.2°	103.8°	102.8°
Counts *in vivo**									
Total leukocyte count	14.6	9.9	3.5	10.0	7.3	4.7	10.1	16.4	11.7
Polymorphonuclears	2.1	3.9	1.8	3.7	4.4	3.9	3.7	4.6	7.2
Lymphocytes	12.3	5.9	1.7	6.1	2.8	0.8	6.0	11.2	4.0
Counts *in vitro*†									
Total leukocyte count	7.4	6.1	6.0	10.0	9.9	9.0	—	—	—
Polymorphonuclears	0.2	0.4	0.3	4.2	3.7	3.4	—	—	—
Lymphocytes	7.1	5.7	5.6	5.8	6.2	5.1	—	—	—
Lysis test changes (per cent)‡									
Total leukocyte count in saline	—	−2.8	+1.6	—	−2.7	−6.5	—	—	—
OT 1:20	—	−8.5	−18.6	—	−3.6	−21.0	—	—	—
OT 1:5	—	−2.2	−7.7	—	−11.5	−39.6	—	—	—
Polymorphs in saline	—	—	+1.6	—	−11.5	+9.3	—	—	—
OT 1:20	—	—	+57.0§	—	+2.6	−35.5	—	—	—
OT 1:5	—	—	+46.2§	—	−15.3	−50.9	—	—	—
Lymphocytes in saline	—	—	+1.6	—	+2.8	−13.3	—	—	—
OT 1:20	—	—	−22.7	—	−8.6	−8.9	—	—	—
OT 1:5	—	—	−11.1	—	−5.6	−30.8	—	—	—

* Bled from ear vein at times indicated. Counts given in thousands of cells.

† Bled from ear vein one or two minutes after OT injection. Blood in siliconed tube rotated once per minute at 37°C.

‡ Bled before OT injection. Saline or OT added to blood *in vitro*. Number 17 was also tested with OT 1:100; no fall was observed.

§ These values are not valid, since the polymorphonuclear count in this animal was too low (approximately 5 per cent) to permit accurate differential counting.

In no instance, however, was there a change in count in blood removed from animals after the OT injection and followed *in vitro*. The fall in leukocyte count in the usual *in vitro* lysis test involved polymorphonuclears and lymphocytes to approximately the same degree and could only be brought about with much higher concentrations of tuberculin than were reached in the animals' bloodstreams with the doses given. The findings are illustrated by typical protocols in tables 8 and 9.

DISCUSSION

The data presented leave little doubt that the capacity to lyse leukocytes in the presence of tuberculin is a property of certain tuberculous rabbit sera.

As previously reported (3, 8, 9), this property is not related to the presence of skin sensitivity to the delayed type. The lytic antibody affects both polymorphonuclear cells and lymphocytes and appears to be thermostable in most instances. In these particulars, except for thermostability, the present data confirm the findings of Favour and his co-workers in tuberculous guinea pigs and mice (10). The experiments do not indicate what method of sensitization is most effective in producing lytic antibody. Repeated intravenous inoculation of dead organisms may result in elevated leukocyte lytic activity which lasts several weeks and is maximal at approximately two weeks. The antibody under investigation appears similar to that produced by immunization with ovalbumin or bovine gamma globulin (1). It seems to differ in that lysis occurs more slowly and involves both polymorphonuclear cells and lymphocytes. Furthermore, antisera against egg albumin or bovine gamma globulin showing lysis can produce urticarial passive transfer of the Prausnitz-Kustner type (1), while this property has not been demonstrated in the sera of tuberculous animals. However, these differences may depend less on actual differences in the antibodies than on the fact that the test antigens in the present study (OT, PPD) contain protein fragments rather than unaltered protein antigens (11).

In an attempt to relate the leukocyte-lysing property to better known antibodies of tuberculosis, it was compared with the erythrocyte agglutinating antibody described by Middlebrook and Dubos (12) and with precipitating and complement-fixing antibody. While a rather complex antigen, namely, Lederle's special Old Tuberculin, was used to determine the presence of these three types of antibody activity, it is known that the erythrocyte-agglutinating activity depends on carbohydrate antigens (13, *see also* 5.) Leukocyte lysis was produced with a fairly homogenous protein antigen, PPD, which is ineffective in causing erythrocyte agglutination (5). The coincidence of leukocyte lysis and erythrocyte agglutination in many of the sera examined suggests that these antibodies are not only similar in their manifestations but also may be produced under similar conditions. The absence of correlation of leukocyte lysis with precipitation or complement fixation, including a number of instances of positive lysis in which neither of the other two serologic properties was found, suggests a diversity of antibodies almost as great as the number of techniques used to recognize them.

It is clear that the changes in blood picture following intravenous tuberculin injection in tuberculin-sensitive rabbits do not depend on the presence of leukocyte lysis of the type studied here. The immediate fall in polymorphonuclear cells is probably comparable to the fall observed in normal animals following intravenous injection of a variety of foreign materials (14, 15) or of histamine (16) and depends on an increased stickiness of these cells (17, 18) and their temporary trapping in the lungs and elsewhere (15, 19, 20). A fall of lymphocytes at six hours, seen in earlier experiments (7, 21, 22) and in the present study, is also seen after injection of sundry foreign and pyrogenic substances (23, 24, 25). The detailed mechanism is not understood; such a fall may occur even in the absence of adrenal cortical activity (26). Whether its occurrence is related to tuberculin shock is a question not within the scope of this paper.

It is pertinent to call attention to the similarity of the cell clumps seen in this

in vitro process to the "rosettes" observed in the so-called "L. E. phenomenon" (27, 28) of disseminated lupus erythematosus. Cells comparable to the "L. E. cell" have not, however, been observed.

SUMMARY

Addition of tuberculin to blood of certain tuberculin-sensitized rabbits results in lysis of leukocytes, which occurs over the course of several hours.

The lysis phenomenon can be demonstrated with purified protein derivative (PPD) as antigen and will occur in fresh normal blood to which a appropriate antiserum has been added.

Both polymorphonuclear leukocytes and lymphocytes are lysed, the former to a greater degree and more rapidly.

The lytic property of the antiserum can be destroyed in some but not in all instances by heat (57°C. for four hours).

The lytic property is not correlated with the characteristic cutaneous sensitivity to tuberculin.

The lytic property is not associated with the presence of precipitating or complement-fixing antibody, but is moderately well correlated with the presence of erythrocyte-agglutinating antibody to tuberculin.

The lytic property differs in thermostability from that found in the blood of tuberculous guinea pigs and mice. It differs in the type of cells affected and in the speed of lysis from the lytic antibody found in rabbits sensitized to purified proteins (ovalbumin, bovine gamma globulin).

The fall in lymphocytes six hours following intravenous administration of tuberculin in tuberculin-sensitive rabbits is not related in any way to the *in vitro* lytic effect observed.

SUMARIO

Comparación de la Leucocitolisis con Ciertos Otros Fenómenos Inmunológicos Observables en los Sueros de los Conejos Tuberculosos

La adición de tuberculina a la sangre de ciertos conejos tuberculino-sensibilizados dió por resultado lisis de los leucocitos, lo cual ocurrió en el transcurso de varias horas.

Este fenómeno lítico puede provocarse con PPD como antígeno y se presentará en sangre normal reciente a la que se haya agregado un antisuero apropiado.

La lisis afecta tanto a los leucocitos polimorfonucleares como a los linfocitos, a los primeros en forma más intensa y con mayor rapidez.

Puede destruirse la propiedad lítica del antisuero en algunos casos, pero no todos, por el calor (57°C. durante cuatro horas).

La propriété lytique et la sensibilité particulière des tissus cutanés pour la tuberculine sont sans corrélation.

La propiedad lítica no va asociada con la presencia de anticuerpo precipitante o fijador del complemento, pero se correlaciona moderadamente con la presencia de anticuerpo eritrocito-aglutinante a la tuberculina.

La propiedad lítica discrepa en termoestabilidad de la observada en la sangre de los cobayos y ratones tuberculosos. Discrepa en la clase de glóbulos afectados y en la celeridad de la lisis, del anticuerpo lítico observado en los conejos a proteínas purificados (ovialbumin, globulina gamma bovina) sensibilizados.

La baja de los linfocitos a las seis horas de la administración intravenosa de tuberculina en los conejos tuberculino-sensibles no se relaciona en modo alguno con el efecto lítico observado *in vitro*.

RESUME

Comparaison entre la lyse du leucocyte et certains autres phénomènes immunologiques démontrables dans le sérum du lapin tuberculisé

L'adjonction de tuberculine au sang de lapins sensibilisés à la tuberculine a provoqué une leucolyse qui s'est manifestée au cours de plusieurs heures.

Le phénomène de la lyse peut être démontré en utilisant le PPD comme antigène; il se produira dans le sang normal frais après adjonction d'un antisérum approprié.

Les polymorphonucléaires et les lymphocytes subissent tous deux la lyse. Les premiers à un degré plus élevé et plus rapidement que les seconds.

L'activité lytique de l'antisérum peut être détruite dans certains cas, mais non dans tous, par le chauffage à 57°C. pendant quatre heures.

La propiedad lítica no está correlacionada con la típica sensibilidad cutánea a la tuberculina.

L'activité lytique n'est pas liée à la présence d'anticorps ayant la propriété de précipiter ou de fixer le complément, mais elle présente une certaine corrélation avec la présence d'anticorps à la tuberculine qui agglutinent les érythrocytes.

L'activité lytique diffère en thermostabilité de celle observée dans le sang des cobayes et des souris tuberculisés. Elle diffère à l'égard du type des cellules affectées et de la vitesse de la lyse provoquée par l'anticorps lytique découvert chez le lapin sensibilisé aux protéines purifiées (ovalbumine, globuline gamma).

La chute lymphocytaire observée six heures après administration intraveineuse de tuberculine au lapin allergique est sans aucune relation avec l'effet lytique observé *in vitro*.

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THE USE OF THE RABBIT EYE AS A TISSUE TO STUDY TUBERCULOSIS[1,2,3]

IV. Effect of Therapy with Streptomycin-Isoniazid and with Growth Hormone (STH) upon the Course of the Infection

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INTRODUCTION

Ocular tuberculosis in the rabbit, when produced by a human strain of *Mycobacterium tuberculosis*, is a reasonably predictable disease (1). The untreated infection has certain characteristics not dissimilar to chronic pulmonary tuberculosis in the human, notably, acute inflammation followed by necrosis, remarkable localizing efforts on the part of the host, final arrest with fibrosis, and in most circumstances, local disease without dissemination. This natural course can be altered appreciably by a variety of drugs.

The present report describes further experiences in the study of ocular tuberculosis in the rabbit. In the study an attempt is made to protect the animal both by a powerful regimen of antituberculous drugs and by stimulating it with a hormone designed to increase its nonspecific defenses against the infection. The effects upon the course of the eye disease of combined therapy with streptomycin and isoniazid[4] and by the administration of pituitary somatotropic hormone are described. This latter effort is predicated on the theory that growth hormone (STH) is capable of increasing the host's ability to produce specific defenses against the infection by its nitrogen-saving mechanism (2).

Because the study necessarily had to be performed in two parts, the observations are recorded individually. Thereafter, an attempt is made to correlate the separate results.

MATERIALS AND METHODS

The methods utilized in the present study were similar to those described previously (1). In brief, adult, mongrel, white rabbits, averaging 3.3 kg. of body weight, were infected by the direct inoculation of approximately one million viable human-strain tubercle bacilli into the anterior eye chamber. The inoculum rarely exceeded 0.05 ml., and the Tween-albumin medium, in which the organisms were cultured, was used as the suspending agent.

The course of the infection was observed in 21 rabbits: 7 were treated with isoniazid-streptomycin combination alone; 5 were treated with somatotropic hormone alone; 4 were

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[3] Presented in part before the Medical Session, as part of the session on *Research*, at the annual meeting of the National Tuberculosis Association, Los Angeles, California, on May 21, 1953.

[4] Streptomycin and isoniazid were both graciously supplied by Dr. Gladys L. Hobby, Charles Pfizer & Co. Inc., Brooklyn, New York.

treated with both the antituberculous drugs and the hormone; and there were 5 controls. No animal was immunized prior to the study with drugs and/or hormones.

All therapy was instituted within twenty-four hours after inoculation of organisms into the eye. Therapeutic regimens were extended for a total period of thirty days. The dosage of streptomycin was 30 mg. per kg. of body weight, given daily in one intramuscular injection. Isoniazid was administered daily in the diet in a dosage of 5.0 mg. per kg. of body weight. Animals received approximately 1 mg. of pituitary growth hormone per day (300 γ per kg. per day).

At autopsy, the weight of the spleen was recorded. This was the only measurement of the effect of growth hormone which was performed upon the animals.

RESULTS

Effect of Streptomycin-Isoniazid Combination

The anterior eye chambers of 10 rabbits were inoculated with approximately one million viable units of human-type tubercle bacilli. Resulting disease in the 3 controls attained an advanced stage within three weeks, a predictable phenomenon (1). Within seventy-two hours after institution of the infection, acute inflammation was noted, which steadily progressed (figures 1*A* and *B*). By the fourteenth day all portions of the anterior segment of the eye were involved (figure 1*A*) and, after three weeks, the normal structures were indistinguishable because of their complete replacement by tuberculous granulation tissue and caseation (figure 1*B*). At autopsy, tuberculous lesions in liver, spleen, and lung were found in 2 of the 3 animals (table 1).

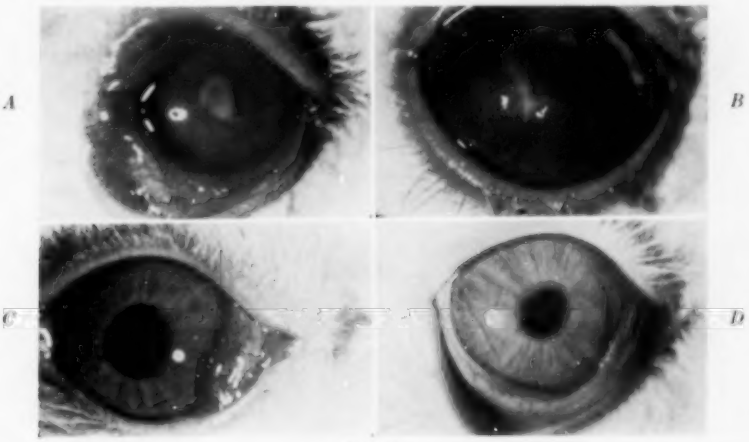

FIG. 1

A. Rabbit eye inoculated seventy-two hours before photograph with plus-minus one million viable human-strain tubercle bacilli. Animal was not treated. Ocular lesion is moderately advanced and the tuberculosis involves anterior chamber and iris.

B. Same eye twenty-one days later. Eye tissue is replaced by acute tuberculous inflammation. This course is typical of that seen in control group.

C. Rabbit eye three days after inoculation of plus-minus one million viable human-strain tubercle bacilli. Animal was treated with isoniazid and streptomycin. Eye is normal.

D. Same eye two weeks later; no disease has developed.

TABLE 1

EFFECT OF THE ADMINISTRATION OF GROWTH HORMONE (STH) AND STREPTOMYCIN-ISONIAZID UPON THE RABBIT WITH OCULAR TUBERCULOSIS

REGIMEN	NUMBER OF ANIMALS	NUMBER WITH ADVANCED EYE DISEASE	NUMBER WITH MINIMAL EYE DISEASE	NUMBER WITH NO EYE DISEASE	NUMBER WITH DISTANT DISEASE AT AUTOPSY	AVERAGE SPLEEN WEIGHT AT AUTOPSY	AVERAGE TOTAL WEIGHT AT AUTOPSY
						gm.	*kg.*
STH alone	5	5	0	0	4	1.62	3.3
STH and streptomycin-isoniazid	4	1*	2	1	0	1.1	3.5
Streptomycin-isoniazid alone	7	1	3	3	0	1.3	3.3
Controls (no treatment)	5	5	0	0	3	1.6	3.0

* Moderately advanced lesion at three weeks.

In impressive contrast, the resulting ocular infections in 6 of 7 rabbits treated with a combination of streptomycin and isoniazid never extended beyond the minimal stage. In 3 of the 6 animals, macroscopic disease failed to develop (figures 1*B* and *C*). In the other 3, minimal disease, represented by small 1 to 2 mm. solid tubercles, developed after a week. In these 3 instances, the lesion had stabilized by the third week, and remained permanently for the life of the animal as a small white isolated tubercle located in the central portion of the anterior chamber. One animal treated with streptomycin-isoniazid did develop advanced disease, similar to that seen in all of the controls. Relapse of infection was not observed in any drug-treated animal following termination of one month's treatment.

Effect of Somatotropic Growth Hormone (STH)

Five rabbits, following institution of ocular tuberculosis, were treated with pituitary growth hormone. Advanced tuberculosis of the orbit developed in all of the 5 within three weeks of inoculation of the organisms. Individual lesions could not be distinguished from those observed in the 2 control animals.

No effect of any kind could be described; the lesions developed as rapidly, extended as far, and disseminated to spleen and lung as frequently as in the control series (table 1). Indeed, when compared with previous experiences in study of rabbit eye tuberculosis, the ocular lesions which developed under the influence of STH were precisely those predicted in control animals (1).

Effect of Combined Drug and Hormone Therapy

With the concomitant administration of STH, isoniazid, and streptomycin, ocular tuberculosis failed to progress beyond the minimal stage in 3 of the 4 animals (table 1). In one of these, no macroscopic disease was observed. The fourth animal developed a moderately advanced lesion by the end of the third week.

Antimicrobial therapy was discontinued after the fourth week, and STH was

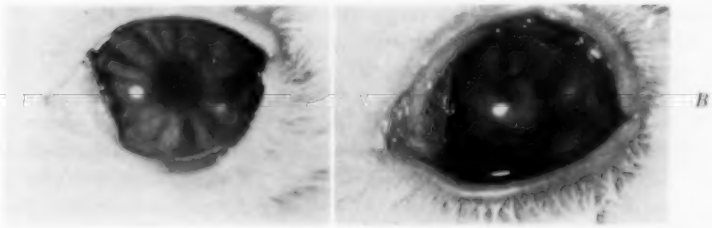

FIG. 2

A. Rabbit eye one week after cessation of one month's therapy with isoniazid and streptomycin, but with continuation of therapy with STH.

B. Same eye three weeks later. Animal still being treated with STH.

continued for a second month. In all 4 animals, the ocular infection relapsed promptly. Within seven days the disease was actively progressing, and thereafter it paralleled precisely disease in the controls (figures 2*A* and *B*). No metastatic lesions were found at autopsy despite the local relapse.

DISCUSSION

The pituitary growth hormone used in the present studies was as purified as it was possible to obtain. It contained 23 mg. of active material per ml.; 10 γ given to hypophysectomized rats caused a growth increment of 1 gm. per day for ten days (5). It was not established, however, that in the production of the material all adrenocorticotropin had been removed. Consequently, the response of the infection following its administration may have been compromised by a foreign substance known to be active in altering unfavorably the course of tuberculosis in the rabbit.

One of the physiologic effects of adrenocorticotropic hormone in an animal is a general catabolic one, with severe and prolonged nitrogen loss. This consequence of its administration, perhaps more than any other single phenomenon, may explain an animal's poor response to tuberculous infection. Somatotropic hormone, on the other hand, presumably has an opposite effect in an animal, namely, that with its administration nitrogen is saved and the animal remains in positive balance. Furthermore, it is possible that, with combined administration of STH and corticotropin, the former material antagonizes directly the catabolic effect of the administration of corticotropin, and the over-all effect is anabolic activity and excitation of nitrogen storage and retention of protein (2, 3, 4). If this be true, then the presumed impure preparations used in these studies might still have been expected to alter favorably the course of the rabbit eye infection, which did not occur.

Selye and associates have reported that the administration of STH to tuberculous rats inhibited proliferation of organisms, encouraged granuloma formation, and, in general, reduced total infection in the tuberculous animal (3). Using similar materials and with the same approximate dosage regimen, these observations have not been substantiated in rabbits with ocular tuberculosis. In fact, it appeared that STH had no effect whatsoever upon the course of the disease,

either a deleterious or a favorable one. Consequently, whether or not growth hormone antagonizes the physiologic effects of corticotropin or excites nitrogen storage in the tuberculous rabbit, it certainly has shown no concomitant effect upon the course of the disease.

It is unknown whether STH was used in proper dosage to assure maximal physiologic effects. It was given in recommended dosage and for periods longer than necessary to stimulate growth of animals (5). Splenic hypertrophy generally occurred with its administration, but the weight was not increased predictably and hypertrophy of the spleen is commonly seen in tuberculous animals. In the amounts used in this study, however, splenic hypertrophy was not evident. Consequently, it can only be presumed that the dosage of STH was sufficient for purposes of the study. It is unfortunate that there is no known dependable test or measurement in adult animals which clearly indicates that a maximal effect of STH has been exerted. It is evident that spleens of animals with minimal or no disease weighed less than those of animals with advanced disease. It can be postulated that the heavier spleens in the control and STH groups were directly due to the presence of tuberculous lesions in the majority of animals in these two groups and were not, therefore, influenced by the hormone alone.

The studies upon STH as described warrant one conclusion: whether or not the treated animal remains in positive nitrogen balance, the retention of protein is not necessarily synonomous with increased ability to defend against a tuberculous infection.

In contrast, with therapy directed specifically against the invading pathogenic microorganisms, the course of the ocular infection in the rabbit was altered impressively. The small amount of disease observed in the majority of animals treated with streptomycin and isoniazid administered together was appreciably less than that noted with any other regimen of antimicrobial agents (1*b*). In the writers' opinion, no other agent used singly or in combination with other drugs has given total protection to a rabbit against the development of tuberculous infection in the eye. Although such did not occur uniformly, it was observed in this small series in approximately one-half of the animals. Furthermore, with the administration of antimicrobial therapy for one month, the combination so controlled the growth of tubercle bacilli in the eye that relapse did not thereafter occur. These observations also deserve one conclusion: the protection offered the tuberculous rabbit by a combination of isoniazid-streptomycin is definitely superior to both the protection produced by any other regimen of antituberculous agents and that obtained with the pituitary hormones so far studied.

SUMMARY

Pituitary growth hormone, in the dosage used, did not alter tuberculosis in the rabbits' eyes from that observed in untreated controls. In contrast, the combination of isoniazid and streptomycin clearly lessened the amount of disease as compared with that in untreated control animals. The antituberculous protection afforded the animal with this combination exceeded that of any antituberculous drug used singly or in combination with others.

To date, the course of ocular tuberculosis in the rabbit can be influenced favorably

only by the administration of antimicrobial agents. Pituitary growth hormones, despite their nitrogen-saving mechanisms, fail to exert demonstrable effects upon the course of this type of experimental tuberculous infection.

SUMARIO

Uso del Ojo de Conejo como Tejido para Estudiar la Tuberculosis: IV. Efecto de la Terapéutica con Estreptomicina-Isoniacida y con la Hormona del Desarrollo sobre la Evolución de la Infección

La hormona hipofisaria del crecimiento, a las dosis usadas, no alteró la tuberculosis del ojo del conejo, de la observada en los testigos no tratados.

En contraposición a esto, la combinación de isoniacida y estreptomicina disminuyó netamente la proporción de enfermedad, de la presente en testigos no tratados. La protección antituberculosa otorgada al animal con esa combinación superó la derivada de cualquier otra droga antituberculosa, usada ya por sí sola o combinada con otras.

Hasta la fecha, no ha podido afectarse favorablemente la evolución de la tuberculosis ocular en el conejo más que con la administración de agentes antimicrobianos. Las hormonas hipofisarias del desarrollo, a pesar de sus mecanismos ahorradores de nitrógeno, no ayudan al animal a defenderse contra la tuberculosis.

RESUME

Utilisatión de l'oeil de lapin comme tissu d'étude de la tuberculose: IV. Action de l'association streptomycine-isoniazide ou du traitement par l'hormone de croissance (STH) sur le cours de l'infection

L'hormone hypophysaire de croissance, aux doses utilisées, ne modifiait pas l'évolution de la tuberculose au niveau de l'oeil du lapin, par comparaison avec les témoins non traités.

Au contraire, l'association isoniazide-streptomycine réduisait nettement l'importance de l'infection, par rapport aux témoins non traités. La protection antituberculeuse conférée à l'animal par cette combinaison thérapeutique dépassait celle de tout autre médicament antituberculeux utilisé séparément ou en association avec d'autres drogues.

Actuellement, seule l'administration d'agents tuberculostatiques permet d'influencer favorablement le cours de la tuberculose oculaire chez le lapin. Les hormones hypophysaires de croissance, en dépit de leur action d'épargne sur l'azote, ne réussissent pas à augmenter les défenses de l'animal contre la tuberculose.

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EFFECT OF ISONIAZID ON THE VIABILITY OF ISONIAZID-SUSCEPTIBLE AND ISONIAZID-RESISTANT CULTURES OF MYCOBACTERIUM TUBERCULOSIS[1]

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INTRODUCTION

It is generally recognized that the death rate of bacteria exposed to unfavorable environmental conditions, such as exposure to bactericidal drugs, is fairly constant throughout the exposure period (1–4). During the course of drug-susceptibility studies, it was noted that the effect of isoniazid on the tubercle bacillus did not follow this general pattern.

The present study is a report on viability changes of freshly isolated isoniazid-susceptible and -resistant cultures of *Mycobacterium tuberculosis* var. *hominis* when exposed *in vitro* to varying amounts of the drug.

MATERIALS AND METHODS

Ten isoniazid-susceptible cultures of tubercle bacilli freshly isolated from humans and growing on Peizer-Schechter agar (5) and on Löwenstein-Jensen medium (6) were used to observe the effect of isoniazid on the viability of the cultures during growth and during a state of rest.

Five strains of freshly isolated isoniazid-resistant tubercle bacilli were studied for the effect of isoniazid on the viability of resistant cultures. The growths used in this test were the fourth successive semimonthly transplants of resistant primary cultures in Proskauer-Beck synthetic medium (7) containing 100 γ of isoniazid per ml.

To examine the survival of actively growing tubercle bacilli exposed to isoniazid, duplicate series of dilutions of drug were prepared in Proskauer-Beck synthetic medium, the final concentrations ranging from 0.1 to 10 γ per ml. The effect of the drug on resting cells of tubercle bacilli was studied by preparing similar duplicate series of drug dilutions in water containing 0.1 per cent of bovine plasma fraction V. Controls consisted of cultures in both substrates without any drug. Plating agar was prepared by adding 2 per cent (final concentration) of granular agar (Difco) and 10 per cent of horse plasma to the Proskauer-Beck liquid medium.

Inocula of *M. tuberculosis* were prepared from each of 10 drug-susceptible strains, grown for fourteen days at 37°C. in several tubes each of Proskauer-Beck medium. The fourteen-day growths of each strain were pooled, centrifuged, and washed once with 0.01 M phosphate buffer pH 7.0. The larger clumps of bacteria in each suspension were allowed to settle out for one half hour. The supernatant suspension of each strain was then decanted and diluted with buffer to match the No. 1 tube of the McFarland scale. One milliliter of this suspension of cells was then added to each tube of 9 ml. of drug-plasma-water substrate for the resting-cell test. The inoculum used for Proskauer-Beck drug medium consisted of 1 ml. of a three-fold dilution of each suspension of tubercle bacilli, which was added to 9 ml. of medium. The inoculated exposure tests were kept in the incubator at 37°C.

The technique for viable counts of drug-treated cells and control cultures (untreated) was a modification of that described by Fenner (8, 9). After thorough mixing, a 0.5 ml. sample was taken from each drug-exposed culture at the end of each exposure period and diluted with 4.5 ml. of 0.01 M phosphate buffer pH 7.0. Further serial 1:10 dilutions were

[1] From the Bureau of Laboratories, Department of Health, New York City.

carried out in the same diluent, depending upon the amount of growth in the exposure tube. Five replicate drops of 0.02 ml. each, from the greatest dilution tube, the next greatest dilution tube, and the original exposure tube, were placed on the surface of a Proskauer-Beck serum agar plate. The plates were kept on the table until the drops were absorbed into the agar. They were then sealed with masking tape and placed in the incubator at 37°C. Growth of colonies of surviving cells appeared in approximately eight days. Colony counts were made at the end of three weeks of incubation by use of a Quebec Colony Counter. At this time the drop cultures were fully grown, with the colonies still discrete. Whenever possible, plates were chosen for counting with counts between 30 and 50 colonies per drop. The number of surviving cells was determined by the average colony count on each plate, multiplied by the appropriate dilution factor.

The study of the effect of isoniazid on drug-resistant cultures consisted of the inoculation of 0.1 ml. of fourteen-day growths of resistant bacilli, which had been incubated at 37°C., into 16.5 × 150 mm. matched test tubes containing 9.9 ml. of Proskauer-Beck medium with varying concentrations of isoniazid. The concentrations of isoniazid used were 0.5, 1.0, 5.0, 10.0, and 25.0 γ per ml. The cultures, prepared in duplicate, were incubated for twenty-one days at 37°C. and were shaken daily to obtain homogeneous growths. The extent of

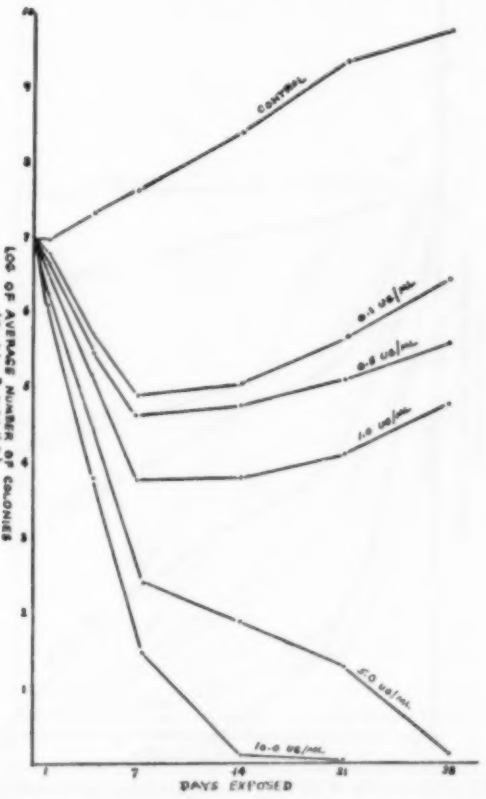

FIG. 1. Survivor curves of actively growing *M. tuberculosis* exposed to isoniazid.

growth was determined by light transmission measurements on the "Lumetron," photoelectric colorimeter, with a matched test tube containing 10 ml. of Proskauer-Beck medium as the control blank adjusted to read 100. Readings were recorded before incubation of the cultures and the amount of growth was determined after one day of incubation, and then every other day. (The light transmission measurements were converted to density values by use of the formula $D = 2\text{-}\log_{10}T$, where D = density and T = light transmission.)

RESULTS

The results of the effect of isoniazid on the viability of actively growing cells are represented in figure 1 and those of resting cells in figure 2. The distorted survivor curves in figures 1 and 2 may probably be attributed to the presence of variation in resistance to isoniazid of the exposed tubercle bacilli. It is of interest that the death rate of exposed organisms did not remain constant.

In general, as seen in figure 1, the bacterial death rate of drug-susceptible actively growing organisms exposed to isoniazid was rapid during the first four

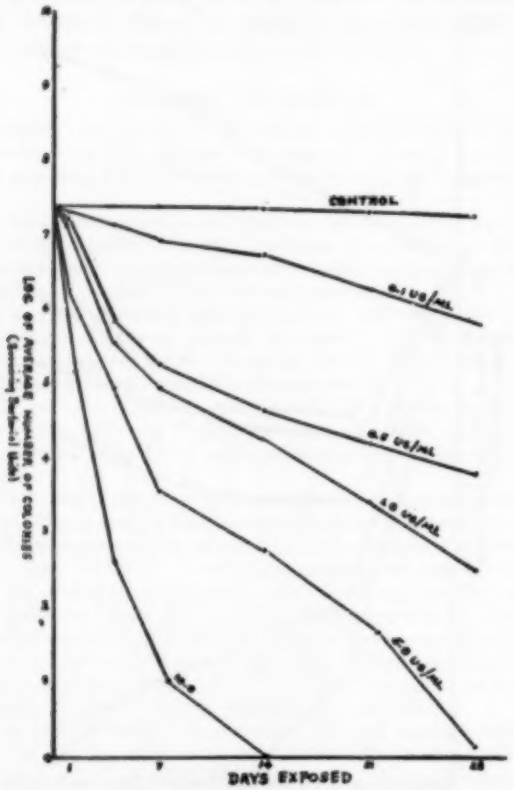

FIG. 2. Survivor curves of resting *M. tuberculosis* exposed to isoniazid.

to seven days, followed by a slower rate until, between the seventh and fourteenth days, the resistant cells took over and obvious growth occurred. Although there was a reduction in the death rate of resting cells (figure 2) after seven to fourteen days of exposure to the drug, the organisms continued to die. This slowing down may have been due to an increase in resistance to isoniazid of the exposed resting cells of tubercle bacilli. This seems to be in agreement with some investigators who worked with streptomycin (12–17), but at variance with the findings of Middlebrook (10) in 1946 and Tisson (11) in 1950, dealing with the effect of streptomycin on resting cells of tubercle bacilli.

From the results obtained in the study of the effect of isoniazid on five drug-resistant strains of tubercle bacilli, it appears that initiation of growth of these cultures was slower in medium containing isoniazid than in medium without drug. The results in figure 3 indicate that the lag phase of resistant tubercle bacilli increased as concentrations of drug in the medium increased.

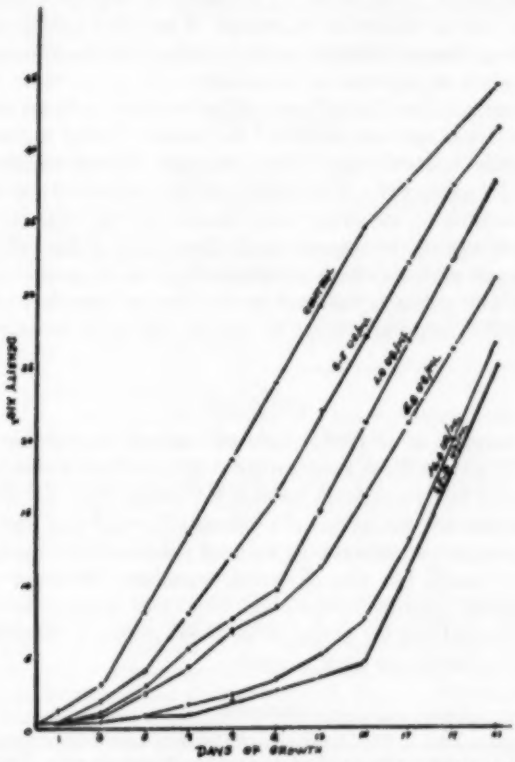

FIG. 3. Average growth curves of five *M. tuberculosis* strains resistant to 100 γ of isoniazid per ml. when exposed to isoniazid.

DISCUSSION

The observations in the present study were based on colony counts resulting from growth of surviving organisms after exposure to isoniazid. It is therefore of importance to note the errors which are usually involved in counting viable organisms of *M. tuberculosis*. This bacillus grows in small loose clumps or flakes in Proskauer-Beck synthetic medium as well as in other liquid media. Daily shaking of cultures helped to break up these aggregates of bacilli into single cells and smaller clumps. Smears of suspensions of tubercle bacilli used as inocula for plate counts in this study showed a large proportion of units consisting of 3 to 15 organisms in every examined inoculum. The plate counts, therefore, represented a record of viable bacterial units rather than of individual organisms. Another error might have arisen from the breaking down of some of the groups of bacilli during the preparation of dilutions for plating, resulting in a higher survivor count. There are also, aside from possible technical errors, considerations of variation in resistance to exposure to isoniazid of individual cells when first exposed (18, 19) and of variations in amount of acquired resistance due to contact with the drug. These variations no doubt influenced the number of survivors after various periods of exposure in this study.

The observations on the effect of isoniazid on resistant cultures raises the question whether true variants are produced in cultures during exposure to isoniazid. It is generally believed that a true resistant variant maintains complete resistance (in this case to 100 γ of isoniazid per ml.) indefinitely in the absence of, or in smaller amounts of, the drug which caused the variation. However, it appears from the results of the present study that many of the individual cells in colonies growing on medium which contains a high concentration of the selective drug are either only partially resistant to the drug or that they revert, some to the drug-susceptible state and some to various grades of incomplete isoniazid resistance (20).

SUMMARY

The rate of survival of 10 freshly isolated isoniazid-susceptible strains of *M. tuberculosis* in Proskauer-Beck medium (actively growing) and in distilled water plus 0.1 per cent of bovine albumin fraction V (resting cells) was observed during exposure to various concentrations of isoniazid. It was found that isoniazid, especially in the higher concentrations, reduced the viability of not only actively growing tubercle bacilli but also of resting organisms. Resistant variants were produced in actively growing cultures and, to a lesser degree, in resting cultures.

Isoniazid prolonged the lag period of isoniazid-resistant cultures of *M. tuberculosis* growing in Proskauer-Beck medium.

SUMARIO

Efecto de la Isoniacida sobre la Viabilidad de los Cultivos Isoniacido-Susceptibles y Isoniacido-Resistentes del Mycobacterium Tuberculosis

Durante la exposición a varias concentraciones de isoniacida, se observó la tasa de sobrevivencia de 10 cepas recién aisladas de *M. tuberculosis* isoniacido-susceptibles en el

medio de Proskauer-Beck (en proliferación activa) y en agua destilada más 0.1 por ciento de la fracción V de albúmina bovina (células en descanso). Notóse que la isoniacida, sobre todo a las concentraciones más altas, reducía la viabilidad de los bacilos tuberculosos no sólo en desarrollo activo sino también en reposo. Se produjeron variantes resistentes en los cultivos en desarrollo activo y, en menor proporción, en los cultivos en reposo.

La isoniacida prolongó el período de retardo de los cultivos isoniacido-resistentes del *M. tuberculosis* sembrados en el medio de Proskauer-Beck.

RESUME

Effet de l'isoniazide sur la viabilité des cultures isoniazide-résistantes ou isoniazide-sensibles du Mycobacterium tuberculosis

Le taux de survie de 10 souches fraîchement isolées de *M. tuberculosis* isoniazide-sensibles cultivées sur milieu de Proskauer-Beck (croissance active) ou dans l'eau distillée avec 0,1% de la fraction V de sérumalbumine bovine (cellules au stade ralenti) a été enregistré au cours de l'exposition à diverses d'isoniazide. Les auteurs ont observé que l'isoniazide, surtout à haute concentration, réduisait la viabilité, non seulement celle des bacilles tuberculeux au stade actif, mais aussi au stade ralenti. Les variants résistants se produisaient dans les cultures au repos.

L'isoniazide prolongeait la phase retard du développement des cultures de *M. tuberculosis* isoniazide-résistant sur milieu Proskauer-Beck.

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Case Reports

NEOPLASTIC INVOLVEMENT OF THE MENINGES WITH LOW CEREBROSPINAL FLUID GLUCOSE CONCENTRATIONS SIMULATING TUBERCULOUS MENINGITIS[1]

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Nonpurulent meningitis is a syndrome which is encountered with relative frequency. It is characterized by clinical signs of meningitis which are usually relatively slow in progression, a subacute course, and cerebrospinal fluid which reveals a pleocytosis composed for the most part of lymphocytes. This syndrome represents the usual association of findings in viral infections of the central nervous system. When the syndrome is accompanied by abnormally low concentrations of glucose in the cerebrospinal fluid, it is generally considered to reflect the presence of a nonviral infection. Thus, cerebrospinal fluid glucose concentrations are heavily weighted diagnostically in differentiating bacterial or mycotic infections from aseptic or viral meningeal processes.

Most of the nonviral infections which characteristically produce nonpurulent meningitis are relatively easy to identify, and include some mycotic infections, *Treponema pallidum*, enterococci, and other bacteria present as a secondary phenomenon to brain abscess (1). As a consequence, when these relatively quickly identifiable causes of nonpurulent meningitis with low cerebrospinal fluid sugar are not found to be present, it is generally assumed that the patient has tuberculous meningitis.

During the past four years, the present writers have observed 3 patients with signs of progressive meningeal involvement and low cerebrospinal fluid sugars who were subsequently found to have neoplastic infiltration of the meninges without evidence of infection. A diagnosis of probable tuberculous meningitis was erroneously made in each case, and all 3 patients received antituberculous therapy. In 2 of the cases, the presence of neoplastic disease was not suspected prior to autopsy. During the preparation of this manuscript, a report by Dodge and Sayre has appeared in the literature describing four patients with diffuse neoplastic involvement of the meninges in whom low cerebrospinal fluid glucose values were obtained (2). In three of the four cases, an awareness of the fact that low cerebrospinal fluid sugars sometimes occur in meningeal neoplasms led to a correct diagnosis. Despite this recognition of the phenomenon, however, it is believed that the fact that meningeal neoplastic disease can so closely mimic tuberculous meningitis is not generally appreciated. Accordingly, the 3 cases observed by the present writers are reported at this time.

CASE REPORTS

Case 1. A 28-year-old Negro laborer was admitted to the Osler wards of the Johns Hopkins Hospital on May 12, 1949, with complaints of progressive lethargy, nausea, and vomiting

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of two weeks' duration. Approximately two weeks prior to admission, the patient had noted the gradual onset of weakness, easy fatigability, and occasional vomiting following meals. Nine days before admission he developed a progressive occipital headache, noted increasing stiffness of his neck, and began to vomit all ingested foods and fluids. Four days before entry he began to have difficulty swallowing, and his family noted that he was increasingly drowsy and that his speech had become blurred and indistinct. He developed a cough productive of mucoid sputum. During his illness he had noted excessive sweating, but no shaking chills.

Physical examination on admission to the hospital revealed a cachetic, lethargic, dysarthric Negro male. The temperature was 101.8°F., the pulse 120, and the respirations 24 per minute, while the blood pressure was 160 systolic and 90 diastolic in mm. of mercury. There was definite adenopathy involving the epitrochlear and inguinal lymph nodes. The abdomen was slightly distended and tympanitic. In the lower right abdomen a hard, grossly nodular, nontender, movable mass could be felt, extending from the level of the umbilicus to the pelvic brim.

The positive neurologic findings were striking nuchal rigidity, papilledema of the left optic nerve head with an adjacent linear hemorrhage in the retina, weakness in the right external rectus muscle, dysarthric speech, and absence of deep tendon reflexes in the lower extremities.

Laboratory studies on admission revealed a negative serologic test for syphilis (Wassermann) and normal values for the erythrocyte count, hemoglobin, and hematocrit. The leukocyte count was 11,700 per cu. mm. with a definite increase in immature granulocytes. Urinalysis showed a 2-plus proteinuria, 2 to 3 leukocytes, and 10 to 15 erythrocytes per high, dry microscopic field, with occasional granular casts. A stool specimen was positive for occult blood by the guaiac reaction. Chemical determination of various constituents of the blood yielded normal values except for an elevated nonprotein nitrogen of 63 mg. per 100 ml. The cutaneous reaction to tuberculin was strongly positive to 0.001 mg. of Old Tuberculin. A chest roentgenogram revealed a suspicious density near the right hilum suggestive of enlarged hilar nodes: there were strandlike densities extending upward into a poorly defined infiltrate in the right apical region. A flat plate of the abdomen revealed a poorly defined mass occupying most of the right abdomen.

On the day of admission, a lumbar puncture was performed which revealed cerebrospinal fluid under increased pressure (450 mm.) and 360 leukocytes, of which 90 per cent were mononuclears. The cerebrospinal fluid protein was 50 mg. per 100 ml.; the glucose, 40 mg. per 100 ml.; and the chlorides were 126 mEq. per liter. No acid-fast bacilli were seen on microscopic examination of the fluid, and it was sterile on culture. On the two subsequent days, lumbar punctures were repeated and blood for sugar determinations was obtained at the same time. These findings may be seen in table 1.

Because of the lymphocytosis and falling cerebrospinal fluid glucose, a diagnosis of tuberculous meningitis and tuberculosis of the mediastinal and abdominal lymph nodes was made. Therapy consisting of dihydrostreptomycin parenterally and streptomycin intrathecally was started. The patient's course was one of progressive decline. Because of frequent retching and his inability to swallow, total feeding by the intravenous route was necessary. A barium enema, performed in an attempt to delineate the abdominal mass, revealed normal filling of the colon. Three days after the institution of chemotherapy, a polyethylene catheter was inserted intrathecally via the third lumbar interspace, and both the parenteral and intrathecal streptomycin dosages were raised because of continued fever and general lack of improvement. Despite intensive therapy, somnolence and opisthotonos increased, and the cerebrospinal fluid glucose continued to fall, reaching concentrations lower than 5 mg. per 100 ml. six days prior to death. A flaccid paralysis of the patient's lower extremities developed, and he died on his nineteenth hospital day. Repeated cerebrospinal fluid cultures for bacteria and fungi and ten cerebrospinal fluid cultures for tubercle bacilli were sterile.

TABLE 1

CEREBROSPINAL FLUID STUDIES

Case 1

DATE	LEUKOCYTES PER CU. MM.	PER CENT MONONUCLEARS	PROTEIN	SIMULTANEOUS BLOOD SUGARS	GLUCOSE
			(*mg. per 100 ml.*)	(*mg. per 100 ml.*)	(*mg. per 100 ml.*)
5/12/49	360	90	50	—	40
5/13/49	480	100	43	96	40
5/14/49	340	100	21*	84	26
5/15/49	156	100	28*	†	100†
5/21/49	—	—	72	72	16
5/23/49	—	—	54	92	13
5/25/49	—	—	108	—	5
5/31/49	119	100	118	152	20†

* Pedicle formation.

† Receiving intravenous glucose.

Post-Mortem Examination

Post-mortem examination revealed a diffuse lymphosarcoma (large-cell type) which involved the lymph nodes and had infiltrated all of the abdominal and thoracic viscera, the bone marrow, brain, spinal cord, and meninges. On gross examination of the brain and spinal cord, the dura mater appeared normal, and the cerebrospinal fluid was clear and colorless. The leptomeninges were milky and opaque, particularly over the frontal, parietal, and occipital surfaces of the frontal lobes. The meninges about the base of the brain showed some violet discoloration, but were not abnormally adherent. Serial coronal sections of the brain and spinal cord showed no gross abnormalities except for some questionable foci of softening in the lumbar and thoracic cord. Microscopic examination of the meninges over the cortex, pons, cerebellum, and cord revealed large collections of cells resembling lymphocytes and lymphoblasts which were similar to those seen in the lymphosarcoma found elsewhere. At all levels there was perivascular cuffing by the same cells within the substance of the brain and cord. There were no giant cells or evidence of tubercle formation. Post-mortem cultures were sterile for *M. tuberculosis* and other bacteria.

Comment: This young Negro male presented with slowly progressive meningeal signs, marked weight loss, an abdominal mass, and generalized lymphadenopathy. Because of low and falling cerebrospinal fluid glucose concentrations in the presence of cerebrospinal lymphocytosis, tuberculous meningitis was believed to be the probable diagnosis. Despite antituberculous therapy, the patient's course was one of rapid decline and death. Post-mortem examination revealed a diffuse lymphosarcoma with involvement of the meninges. These was no evidence of meningeal infection, and post-mortem cultures of the cerebrospinal fluid were sterile.

Case 2. A 55-year-old white woman was admitted to the New York Hospital-Cornell Medical Center[1] on June 29, 1948, with complaints of nausea, vomiting, facial asymmetry, and unsteadiness of gait of nine days' duration. Three weeks prior to admission the patient had noted increasing fatigue and had developed a dull, aching pain in both posterior thighs which became worse at night and appeared unrelated to position, coughing, or straining. Nine days before entry, she developed nausea and vomited many times. This recurred two days later and was associated with mild vertigo and a staggering gait which persisted until the time of admission. Seven days before admission the patient noted that the right

[1] This case is reported through the courtesy of Dr. Helen Haskell.

TABLE 2

CEREBROSPINAL FLUID STUDIES

Case 2

DATE	LEUKOCYTES PER CU. MM.	PER CENT MONONUCLEARS	PROTEIN	GLUCOSE
			(*mg. per 100 ml.*)*	(*mg. per 100 ml.*)
7/1/48	414	9	111	6
7/2/48	1,396	68	20	7
7/4/48	1,090	100	20	5
7/6/48	761	100	99	5
7/8/48	1,950	100	—	5
7/9/48	893	100	120	1
7/10/48	670	100	10	6
7/11/48	2,000	90	—	68†
7/12/48	1,428	93	3	8
7/14/48	1,472	98	12	29
7/16/48	1,720	93	0	13

* It is believed that pedicle formation was responsible for the wide swings in cerebrospinal fluid protein.

† May have been receiving IV glucose.

side of her face appeared paralyzed. At this time she also developed a nasal quality to her voice and had difficult in swallowing, with regurgitation of fluids through the nose. She noted a tendency to fall to the left on walking and complained of moderate frontal headache. There had been a weight loss of approximately 10 pounds during the previous six months. There was no family history of, or known contact with, tuberculosis.

Physical examination revealed a well-developed woman who was somewhat hyperkinetic, but who did not appear acutely ill. Her temperature was 98.8°F., the pulse was 112, respirations 16 per minute, and the blood pressure 120 systolic and 80 diastolic in mm. of mercury. General examination disclosed no significant findings. Neurologic examination revealed a slow, unsteady gait with a positive Romberg, the patient falling to the left. There was nystagmus on left lateral and vertical gaze, and the left optic nerve head showed marginal blurring. The right corneal reflex was markedly diminished, and there was evidence of left-sided palatal weakness. The tongue deviated to the left on protrusion, and some ataxia was noted on the right finger-to-nose test. The neck was definitely stiff on flexion.

Laboratory studies showed a normal hemogram and a negative serologic test for syphilis (Mazzini). Urinalysis revealed a trace of albumin. Roentgenograms of the chest and skull showed no evidence of infiltrate or tumor. The cutaneous reaction to tuberculin was positive to 0.01 mg. of Old Tuberculin. A lumbar puncture on the first hospital day revealed a pressure of 120 mm. of cerebrospinal fluid, 414 leukocytes, of which 90 per cent were polymorphonuclear leukocytes. The cerebrospinal fluid protein was 860 mg. per 100 ml., and the glucose was reported as 6 mg. per 100 ml. (table 2). No acid-fast bacilli were seen on microscopic examination of the fluid, and cultures were sterile. Special cultures for *M. tuberculosis* were not made at this time.

It was initially believed that this patient had a cerebellopontine angle tumor on the right. However, the results of the initial and subsequent lumbar punctures with progressive lymphocytosis, falling glucose concentrations in the cerebrospinal fluid, and the development of fever convinced all who saw her that the illness represented an atypical meningitis. A viral meningitis was considered, but the possibility was discarded in the face of the consistently low cerebrospinal fluid sugar. The presence of tuberculous meningitis was believed to be probable, and streptomycin therapy, by both parenteral and intrathecal routes, was instituted. Because of the uncertainty of the diagnosis, sulfadiazine and large-dose peni-

TABLE 3

CEREBROSPINAL FLUID STUDIES

Case 3

DATE	LEUKOCYTES PER CU. MM.	PER CENT MONONUCLEARS	PROTEIN	GLUCOSE
			(*mg. per 100 ml.*)	(*mg. per 100 ml.*)
4/9/51	270	100	200	41
4/10/51	212	100	170	21
4/11/51	185	100	180	20
4/12/51	131	100	169	29
4/20/51	138	100	174	40
4/23/51	57	100	157	45
5/1/51	39	100	150	67
5/8/51	70	100	162	48

cillin therapy intramuscularly were also initiated. Despite the intensive antimicrobial therapy, the patient failed rapidly. She developed a bilateral aspiration pneumonia, and died of respiratory failure on the nineteenth hospital day. Repeated smears, cultures, and animal inoculation of the cerebrospinal fluid were negative for bacteria, fungi, and tubercle bacilli. Special studies of the cerebrospinal fluid for several viral agents were also negative.

Post-Mortem Examination

Post-mortem examination revealed an undifferentiated malignant tumor which involved the meninges about the brainstem and spinal cord. On microscopic examination, the meninges at the base of the brain appeared slightly thickened, with small, scattered areas of opacity. The ventricular fluid was cloudy and translucent. Microscopically, the meninges were infiltrated by irregular neoplastic cells undergoing frequent mitoses. Tumor cells were also found densely infiltrating the cerebellar cortex and extending into the brainstem about and within cranial and spinal nerve roots. The lungs contained a massive, confluent pneumonia, from which *Monilia* were cultured. No primary source of the malignancy could be discovered. Post-mortem cultures of the cerebrospinal fluid were sterile.

Comment: This 55-year-old white woman presented with signs suggestive of an intracranial tumor mass and minimal meningeal signs. Because of the marked reduction in cerebrospinal fluid glucose, a chronic bacterial meningitis, most probably tuberculous, was suspected and appropriate therapy was initiated. There was no alteration in the patient's course, and she died on the nineteenth hospital day. Post-mortem examination revealed an undifferentiated malignant tumor which had infiltrated the meninges and cerebellar cortex, extending into the brain stem along cranial nerve roots. Post-mortem cerebrospinal fluid cultures were sterile.

Case 3. An 8-year-old schoolboy was transferred to the New York Hospital-Cornell Medical Center on April 12, 1951, with complaints of headache and diplopia of two weeks' duration. Two weeks prior to admission the patient had developed a constant bifrontal headache which steadily increased in severity. One week preceding admission he began to have episodes of diplopia and intermittent projectile vomiting. He developed remittent afternoon fever, and was admitted to an outside hospital where strabismus, a stiff neck, drowsiness, and a temperature of 101°F. were noted. Three lumbar punctures were performed on successive days and revealed an elevated cerebrospinal fluid pressure, increased leukocyte count, and an elevated cerebrospinal fluid protein. The second and third cerebrospinal fluid examinations also revealed significantly reduced glucose values of 21 and 20 mg. per 100 ml., respectively (table 3). As a consequence of these findings, the patient was

started on a course of parenteral dihydrostreptomycin and sulfadiazine, and his temperature returned to normal. On his fourth hospital day he was transferred to the New York Hospital because of the possibility of underlying tumor. The past and family history were noncontributory and, in particular, there was no history of tuberculosis.

Physical examination revealed a well-developed, apprehensive, and hyperirritable young male who appeared moderately ill. The temperature was 100.1°F., the pulse 92, and the respirations 22 per minute, with blood pressure 122 systolic and 70 diastolic in mm. of mercury. There was generalized cutaneous hyperasthesia. The neck was rigid to forward flexion, and both Kernig and Brudzinski signs were present. There was a bilateral palsy of the sixth cranial nerve, and fundoscopic examination revealed bilateral papilledema. The remainder of the physical examination was not remarkable.

Laboratory studies upon admission included a negative serologic test for syphilis (Mazzini), a normal hemogram except for a mild anemia, and a normal urinalysis. Fasting blood sugars were 88 and 116 mg. per 100 ml. on two occasions. The cutaneous reaction to tuberculin was positive to 1.0 mg. of Old Tuberculin. Following a right parietal burr hole, a lumbar puncture was performed which revealed an initial pressure of more than 600 mm. of cerebrospinal fluid, which contained 160 mg. of protein per 100 ml., 131 leukocytes per cu. mm., all of which were mononuclear, and a glucose concentration of 29 mg. per 100 ml.

At this time it was believed that the most likely diagnostic possibilities were tuberculous meningitis or brain tumor. Ventriculograms were performed which failed to reveal a filling defect, and a subtemporal decompression was subsequently carried out. On observation without antimicrobial therapy, the patient showed gradual improvement. The cerebrospinal fluid glucose values rose to low normal limits, and the cerebrospinal fluid pressure and the patient's temperature returned to normal. The values for cerebrospinal fluid protein and leukocytes remained elevated. It was believed, in view of the patient's improvement, that he probably had a viral encephalitis, and he was discharged on May 9, 1951, to be followed by his private physician. All complement fixation and neutralization tests for known viral agents performed with his cerebrospinal fluid were subsequently reported negative. Four cultures of the cerebrospinal fluid were negative for *M. tuberculosis*.

Five months later the patient was readmitted to the hospital because of bulging of the decompression site, a convulsive episode, and the return of afternoon fever. Ventriculograms performed on this admission revealed a large filling defect obliterating the left ventricular system. Craniotomy was performed, and a large inoperable tumor mass was found which was extensively infiltrating the left temporal lobe. Microscopic examination of biopsied tumor tissue revealed solid masses of cells without a definite structural pattern. Many of the cells had large, darkly staining nuclei and scant cytoplasm. Giant cells with multilobulated nuclei were common. The microscopic diagnosis was Hodgkin's sarcoma. Lumbar punctures performed during this admission continued to show a pleocytosis and elevated protein in the fluid, but, unfortunately, no further glucose determinations were made.

Following operation the patient showed little change, and he was again discharged under the care of his private physician. During the next few weeks he developed massive cervical adenitis, hepatosplenomegaly, and he died one month following his discharge from the hospital. A necropsy performed elsewhere, and which did not include examination of the brain, revealed Hodgkin's involvement of one kidney and the abdominal and mediastinal nodes.

Comment: This 8-year-old male was admitted to an outside hospital with symptoms and signs of increasing intracranial pressure and meningeal irritation. Low cerebrospinal fluid glucose values were obtained on two occasions accompanied by cerebrospinal lymphocytosis, and the patient received a short course of dihydrostreptomycin and sulfadiazine. Confirmation of the low cerebrospinal fluid sugar upon his transfer to the New York Hospital led to serious consideration of tuberculous meningitis. Because of his spon-

taneous improvement without therapy, a viral encephalitis was believed probable at the time of his discharge. Readmission five months later revealed a large intracranial tumor mass infiltrating the left temporal lobe. Microscopic examination of biopsy specimens identified this as a Hodgkin's sarcoma. The diagnosis of Hodgkin's disease was confirmed at post-mortem examination one month later, but no examination of the brain was performed. All cultures of his cerebrospinal fluid made upon his initial admission were sterile. Complement fixation and neutralization tests against known viral agents performed at this time were also negative.

GENERAL COMMENT

The mechanism responsible for the reduced concentrations of cerebrospinal fluid glucose in these 3 patients with neoplastic invasion of the meninges is not known. It has been stated that the subnormal cerebrospinal fluid sugar concentrations observed in bacterial meningitis are the result of glucose utilization by the microorganisms with no significant utilization by the leukocytes (1). Several investigators, however, have presented evidence that glucose is utilized when cerebrospinal fluid-leukocyte mixtures are incubated in the absence of bacteria (3, 4). Goldring and Harford have recently reported observations on this subject, using quantitative techniques. These investigators found that both polymorphonuclear leukocytes and bacteria appear to utilize cerebrospinal fluid glucose, but in amounts insufficient to explain the extremely low concentrations which are found in bacterial meningitis (5). It has been suggested that alterations in the permeability of the blood-cerebrospinal fluid barrier may act to reduce the glucose concentrations in bacterial meningitis (3, 4). Recent studies by Sifontes, Williams, and Lincoln (6) appear to substantiate such a concept, demonstrating a decrease in the exchange of infused glucose from the blood to the cerebrospinal fluid during the acute phase of tuberculous meningitis.

In patients with diffuse neoplastic involvement of the meninges, Dodge and Sayre (2) suggest that simple mechanical blockage of the membrane due to the presence of tumor may prevent sugar from crossing the blood-cerebrospinal fluid barrier in sufficient quantities to maintain the normal ratio between serum and cerebrospinal fluid glucose. It has long been known that tumor cells exhibit atypical carbohydrate metabolism, showing a pronounced degree of anaerobic glycolysis. Such tumor tissue metabolizes glucose at greatly increased rates when compared with normal epithelial cells *in vitro* (7). It is possible, therefore, that the low values for glucose in the present 3 cases with extensive neoplastic involvement of the meninges were due in part to the increased glycolytic rate of the infiltrating malignant cells. Reduction in the permeability of the meninges secondary to malignant infiltration might have aided this process.

It has been the writer's experience that tuberculous meningitis rarely occurs in adults in the absence of demonstrable tuberculosis elsewhere, although in occasional cases such extrameningeal foci are difficult to detect. It seems clear that the possible presence of neoplastic meningeal disease should be considered in patients with nonpurulent meningitis which is accompanied by a low concentration of glucose in the cerebrospinal fluid, and in whom evidence of tuberculosis of extrameningeal sites is lacking.

SUMMARY

Three cases of neoplastic meningitis have been presented in which low concentrations of glucose in the cerebrospinal fluid in the presence of nonpurulent meningitis led to the erroneous diagnosis of tuberculous meningitis. The 3 cases represent additional documentation of the observation that low values for cerebrospinal fluid glucose may be found with

malignant invasion of the meninges in the absence of bacterial infection. This diagnostic possibility should be borne in mind in the presence of the syndrome of nonpurulent meningitis when a low cerebrospinal fluid concentration of glucose is present.

SUMARIO

Invasión Neoplásica de las Meninges con Concentraciones Bajas de Glucosa en el Líquido Céfalorraquídeo Simulando Meningitis Tuberculosa

En los 3 casos descritos de meningitis neoplásica, las bajas concentraciones de glucosa en el líquido céfalorraquídeo coexistiendo con meningitis no purulenta condujeron al diagnóstico erróneo de meningitis tuberculosa. Los 3 casos aportan nueva prueba de que pueden descubrirse cifras bajas de glucosa céfalorraquídea en la invasión maligna de las meninges sin haber infección bacteriana. Debe tenerse presente esta posibilidad diagnóstica cuando exista un síndrome de meningitis no purulenta, si se observa una baja concentración de glucosa en el líquido céfalorraquídeo.

RESUME

Lésions néoplastiques des méninges avec concentration basse du glucose dans le liquide céphalo-rachidien simulant la méningite tuberculeuse

Observation concernant trois cas de méningite néoplastique dans lesquels l'abaissement de la concentration du glucose dans le liquide céphalo-rachidien, en présence d'une méningite non pyogène, conduisit au diagnostic erroné de méningite tuberculeuse. Les trois cas représentent un document additionnel à l'observation qu'en l'absence d'une infection bactérienne on peut rencontrer une faible concentration du glucose dans le liquide céphalo-rachidien quand les méninges sont envahies par des cellules malignes. En présence d'un syndrome de méningite non pyogène, quand la concentration du glucose dans le liquide céphalo-rachidien est faible, il y a lieu de considérer ce diagnostic.

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LUNG CYST INFECTED BY M. TUBERCULOSIS[1]

Report of a Case

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INTRODUCTION

A recent search of the literature has been made to find if a cyst of the lung has ever become infected with *Mycobacterium tuberculosis*. In the recent literature no cases were found except those reported by Rothstein and Moberly (1) and one case from the Massachusetts General Hospital (2). The inclusive term "cyst" is used to designate a sac containing air and/or liquid. The cyst might represent cystic disease, either congenital or acquired, or emphysematous bullae or blebs. The following case report demonstrates that a cyst can become infected with *M. tuberculosis* and clinically simulate an acute nonspecific infection.

CASE REPORT

The patient was a 33-year-old white male, married, service station attendant, who had been discharged from the Army in November, 1947, with the diagnoses of lung cyst and inactive tuberculosis. These diagnoses were based entirely on roentgenographic findings on separation from the service. A chest roentgenogram taken on October 22, 1948, showed increased aeration with reticular markings throughout the entire upper half of the right lung field. Linear densities compatible with fibrotic pulmonary tuberculosis were present in the left upper lung field (figure 1).

He remained in good health until April 23, 1949, at which time he experienced fever to 103°F., chills, nonproductive cough, and malaise, but continued to work for three days. He then consulted a physician, who gave him daily injections of 300,000 units of procaine penicillin for five days. His illness continued unabated, and he was admitted to Birmingham Veterans Administration Hospital on May 3, 1949.

The patient was a well-developed, well-nourished, acutely ill 33-year-old white man. His temperature was 101°F. The thorax was asymmetrical. The right chest appeared smaller and showed delayed and diminished expansion. There was dullness to percussion over the right upper lung field anteriorly and posteriorly with diminished breath sounds over these areas. No rales were heard. The rest of the physical examination was not remarkable.

On admission, the hemogram showed 4,150,000 erythrocytes per cu. mm., 12.8 gm. of hemoglobin, and a erythrocyte sedimentation rate of 46 mm. per hour uncorrected (Wintrobe method). The leukocyte count was 14,200 per cu. mm., with a differential of 77 per cent neutrophils, 17 per cent lymphocytes, 5 per cent monocytes, and 1 per cent eosinophils. The urine had a specific gravity of 1.020, a pH of 5.0, and did not contain any albumin, sugar, or formed elements. The serologic test for syphilis and the complement fixation tests for Q fever, psittacosis, and influenza were negative. The cold agglutinin titer was zero. The tuberculin skin test using second-strength PPD was positive. The coccidioidin skin test using 1:100 strength was negative. Bronchoscopy on May 5, 1949, revealed blunting of the septum of the right upper lobe bronchus, with mild hyperemia and edema within the right upper lobe bronchus. No biopsy was done. Aspirated secretions showed only normal epithelial cells. Three gastric cultures on May 9, 10, and 12, 1949, were reported negative for *M. tuberculosis*.

The patient was treated with bed rest, fluids were forced, and antimicrobial therapy was

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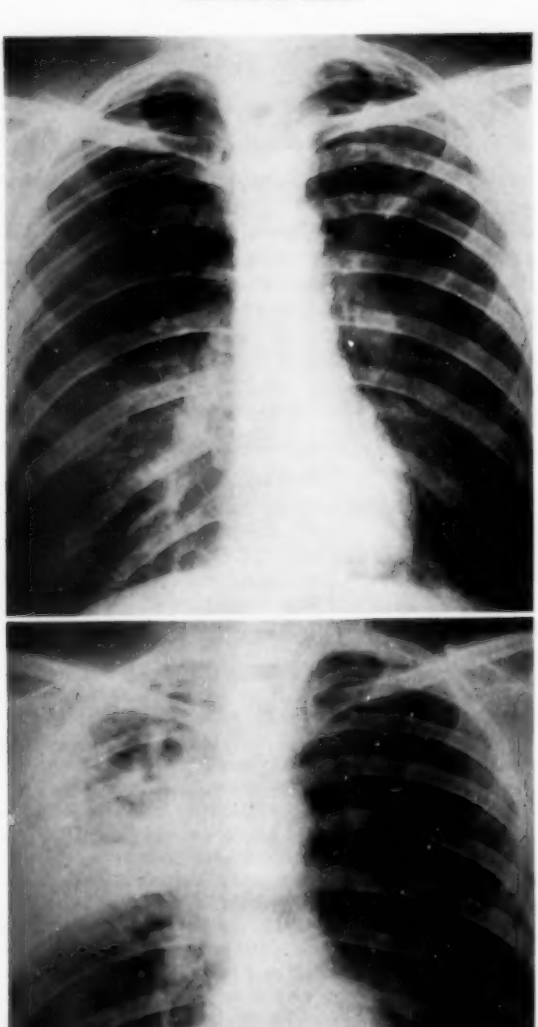

FIG. 1. (Top) Postero-anterior roentgenogram, showing a cyst in the upper half of the right lung and linear densities in the left apex.

FIG. 2. (Bottom) Postero-anterior roentgenogram, showing a homogeneous density in the upper half of the right lung, with a fluid level and multiple lucencies at the right upper apex. Linear densities are present in the left apex.

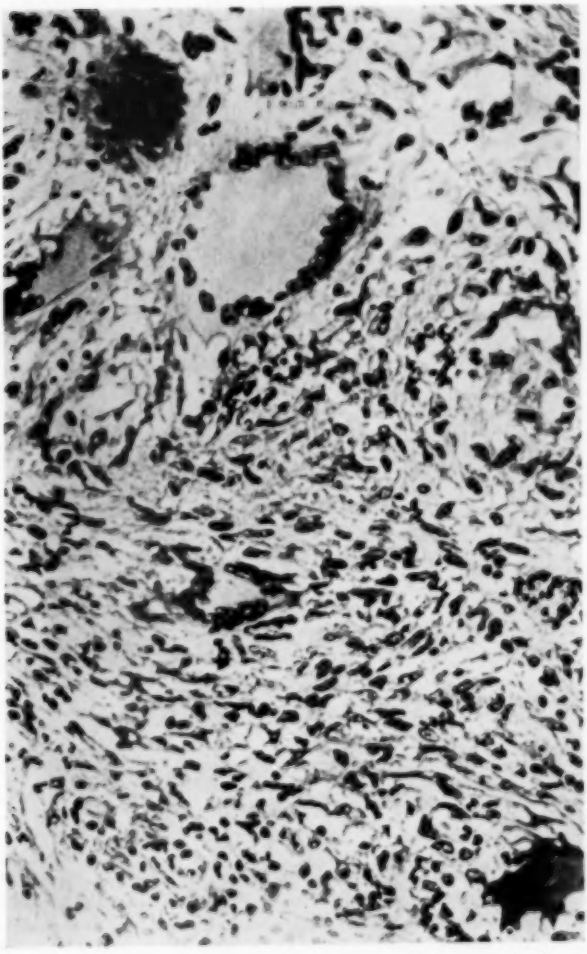

FIG. 3. Portion of the tissue removed at thoracotomy, showing the lung parenchyma diffusely replaced by fibrous tissue in which conglomerate tubercles composed of epithelioid cells and Langhans' giant cells are present. Centers of caseation necrosis are noted.

given as follows: 300,000 units of procaine penicillin G with 1 gm. of streptomycin intramuscularly daily, 4 gm. of sulfadiazine initially by mouth then 1 gm. four times daily for one month. For a period of three weeks the patient was given micronized penicillin, 100,000 units three times daily. The temperature rose to 103.2°F. on the second hospital day and then gradually subsided, reaching 99.6°F. on the twenty-second hospital day, at which level it remained.

The roentgenogram on admission showed a large homogeneous density involving the upper half of the right lung. The lower border was convex. The right apical area demonstrated multiple lucencies suggestive of loculation with a fluid level below the clavicle.

The clinical impression at that time was that the patient had an infected lung cyst. The linear fibrotic densities in the left upper lobe were considered compatible with an old tuber-

FIG. 4. Follow-up postero-anterior roentgenogram, showing a right thoracoplasty and diminution of the linear densities in the left apex.

culous process (figure 2). Repeated roentgenograms revealed variation in the fluid level and areas of density in the right upper lobe.

On July 1, 1949, a thoracotomy was done with the intention of removing an acute non-specific infected cyst. At operation, the right upper lobe was found to be caseous, necrotic, and gangrenous, and contained approximately 90 cc. of pus. It was firmly adherent to the chest wall, so that on entry into the thoracic cage this area was inadvertently entered. As much of the material as could be obtained without danger of hemorrhage was removed by curettement and was forwarded to the laboratory for culture for *M. tuberculosis* and histopathologic examination. The wound was left open with a large drain placed in the area. The patient responded well to this surgical procedure, but his bronchopleural fistula persisted. Thoracoplasty of the right upper chest with removal of ribs two through six was performed in stages on September 7, 1949, and October 4, 1949.

Histopathologic examination of the tissue removed at thoracotomy revealed the lung parenchyma diffusely replaced by fibrous tissue in which conglomerate tubercles were present, consisting of epithelioid cells and Langhans' giant cells. Centers of caseation necrosis were present (figure 3). Culture of the excised lesion was positive for *M. tuberculosis*.

Following the operative procedures, positive cultures for *M. tuberculosis* from material collected from the sinus drainage as well as the gastric washings were obtained for the first time.

Initially it was thought that lobectomy would have to be performed to obliterate successfully the bronchopleural fistula. However, the patient has shown progressive improvement, the fistula has closed, and the remaining caseous mass has contracted. It is now believed that no further surgery is indicated. The last reported positive culture for *M. tuberculosis* was

in July, 1951. The patient was on a medical regimen of 1 gm. of streptomycin twice weekly plus 12 gm. of para-aminosalicylic acid daily from August 17, 1951, until August 29, 1952. Pneumoperitoneum was established on September 18, 1951, and has been continued to date. He has been ambulatory since August 29, 1952 (figure 4).

COMMENT

Others have discussed the diagnosis, pathogenesis, and treatment of lung cysts (3–7). Secondary pulmonary suppurative infection frequently involves cysts and is often the means by which they are first detected. Inasmuch as cysts are prone to infection, it seems not unusual for a cyst to become involved by tuberculosis. This would appear likely in the presence of tuberculosis elsewhere in the lungs.

It is often difficult to determine the exact nature of the cyst by means of histologic examination even in the absence of infection. In the case presented, since there was a superimposed infection with tuberculosis, such histologic identification was impossible.

Emphysematous bullae and blebs as well as congenital and acquired cystic disease may occur in a part of a lung without generalized pulmonary involvement. Hence, from the roentgenographic standpoint, exact determination of the nature of the cyst is also subject to conjecture.

The case presented emphasizes that a tuberculous etiology should be considered in an infected lung cyst, especially if there be roentgenographic evidence of tuberculosis elsewhere in the lungs.

SUMMARY

A case of specific infection of a lung cyst by *Mycobacterium tuberculosis* is presented. Among the various causes of an infected lung cyst, tuberculosis should be considered, especially if there be tuberculosis elsewhere in the lungs.

SUMARIO

Quiste Pulmonar Infectado por M. Tuberculosis

Preséntase un caso de infección específica de un quiste pulmonar por el *M. tuberculosis*. Entre las varias causas de la infección de un quiste pulmonar, hay que considerar la tuberculosis, máxime si existiere esa enfermedad en alguna otra parte de los pulmones.

RESUME

Kyste du poumon infecté par le M. tuberculosis

Un cas d'infection spécifique d'un kyste pulmonaire par le *M. tuberculosis* est présenté. Parmi les différents cas d'infection d'un kyste du poumon, il y a lieu de considérer le diagnostic de tuberculose, surtout en présence d'un autre foyer de tuberculose dans le poumon.

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PERIPHERAL LIPOMA OF THE LUNG[1]

Report of a Case

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In 1951, Touroff reported a case of peripheral lipoma of the lung and briefly reviewed the literature (1). Prior to Touroff's paper, there had apparently been only one similar report (2), although Watts and his co-workers had reported a number of lipomas arising in major bronchi (3). Because of the rarity of this tumor in the periphery of the lung, the following case is deemed worthy of record.

CASE REPORT

W. J., a 46-year-old, white, male physician was admitted to The Hospital of St. Raphael on July 6, 1952 because of hemoptysis. Approximately seven or eight months prior to admission he had noted an increase in his "chronic cigarette cough." The cough was productive of a small amount of mucoid sputum. Two weeks before admission he first noticed blood-streaking of the sputum following a rather violent coughing spell. The remainder of the present history as well as the past medical history was noncontributory. The patient smoked one to two packs of cigarettes daily for many years.

Physical examination was entirely normal. Likewise, the results of the laboratory examination were within normal limits. Roentgenography of the chest demonstrated a small, rounded, well-circumscribed lesion in the apical-posterior segment of the left upper lobe (figures 1, 2, and 3). In retrospect, it is possible that the early manifestations of the lesion were present in a routine chest roentgenogram made on October 18, 1949.

On July 8, 1952, a left upper lobectomy was done. Examination of a frozen section suggested that the tumor was a lipoma. The patient made an uneventful recovery and was discharged from the hospital ten days later.

The resected specimen was a firm, encapsulated nodule 1.5 cm. in diameter in the apical portion of the apical-posterior segment of the left upper lobe (figure 4). Incision over this area showed the cut surface to have a bright orange, somewhat greasy, appearance. Microscopic sections substantiated the diagnosis of lipoma (figure 5).

COMMENT

Watts and his co-workers studied sections from a number of lungs stained with Herzheimer's scarlet red solution in an effort to determine the origin of fatty bronchial and pulmonary tumors (3). They found that fat was normally present in the submucosa and in the fibrous tissue external to the cartilage plates of both the larger and smaller bronchi. Lipomas which occur in the lung parenchyma could, therefore, arise from the fat which is present in the smaller peripheral bronchi. Likewise, the presence of fat in other tumors of the lung, such as hamartomas and adenomas, may be similarly explained.

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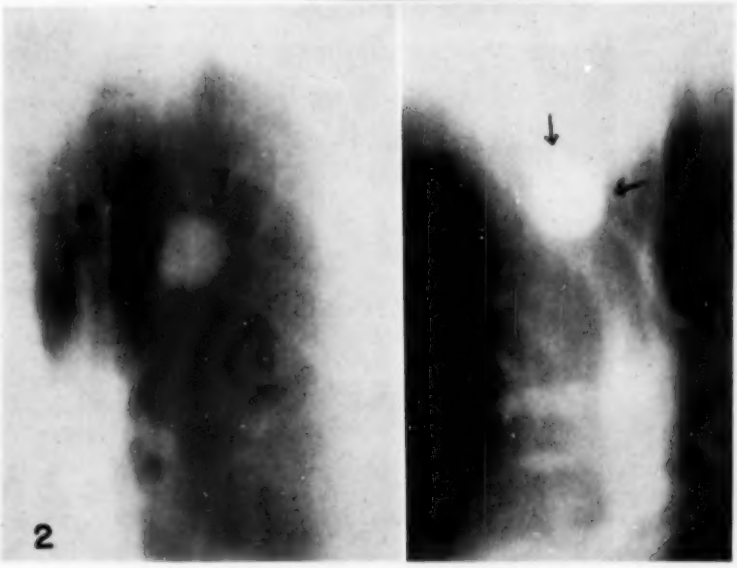

FIG. 1. Conventional postero-anterior roentgenogram of the left upper lobe lesion.
FIG. 2. Antero-posterior planigram of the left upper lobe showing the lesion.
FIG. 3. Lateral planigram of the lesion.

FIG. 4. Photograph of the resected left upper lobe, demonstrating the lipoma which has been sectioned in half.

FIG. 5. Low-power photomicrograph of a section of the lipoma showing normal lung parenchyma at the periphery of the tumor.

TRANSDIAPHRAGMATIC EVENTRATION OF PERITONEUM SECONDARY TO PNEUMOPERITONEUM[1]

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INTRODUCTION

Artificial pneumoperitoneum is widely used in some areas of the United States in the therapy of pulmonary tuberculosis. It is maintained in the great majority of cases without significant deleterious side effects. Nevertheless, in a review of the literature, Stein (1) lists more than forty different complications which may be encountered during the course of artificial pneumoperitoneum. One of these is spontaneous pneumothorax. Ross and Farber (2) have collected twenty cases (including three of their own) of this complication. The case reported by Yannitelli and associates (3) terminated in sudden death, and at post-mortem examination a right pneumothorax under positive pressure was found. Wu and Neptune (4) and Repa and Jacobson (5) have reported two additional cases. In the latter case, the authors believed that a fatal outcome was prevented by the prompt evacuation of 2,250 cc. of air from the right pleural cavity. The various writers cited (1–5) have discussed the possible mechanisms by which the spontaneous pneumothorax comes about secondary to the pneumoperitoneum. The present case is reported as an illustration of what may be the necessary preliminary condition leading to the complicating spontaneous pneumothorax.

CASE REPORT

The patient, N.V., was a 27-year-old, white, male warehouse worker, who had had a routine mobile unit chest film taken on June 12, 1950, at which time he was told that he had "probable tuberculosis." He was referred to this hospital for further examination, and was admitted on November 23, 1950. At that time he was completely asymptomatic, and there was no known exposure to tuberculosis.

Physical examination revealed a well-developed, well-nourished male who did not appear acutely or chronically ill. The systolic blood pressure was 130 mm. and the diastolic pressure was 74 mm. of mercury. Complete physical examination was normal in every respect. The lungs were clear to percussion and auscultation, and no rales were present. Breath sounds were vesicular bilaterally. The chest film of November 22, 1950, revealed mixed infiltration within the right upper lobe between the first and fourth anterior ribs. The rest of the lung fields were clear except for a primary complex beneath the right sixth anterior rib. Five sputum specimens were obtained for concentration and culture. Four of these were negative and the fifth revealed a growth of 5 colonies of tubercle bacilli.

Treatment consisted of bed rest. Because an additional sputum culture was reported positive for tubercle bacilli and a spread of exudative tuberculous disease into the right midlung field was seen, a pneumoperitoneum was induced on March 22, 1951. Subsequently (November, 1951) a right pleural effusion developed, and streptomycin in dosage of 1 gm. intramuscularly twice weekly and para-aminosalicylic acid, 12 gm. by mouth daily, were instituted.

A chest film of January 15, 1952, revealed for the first time a questionable lucency beneath (i.e., behind and below) the highest level of the diaphragm (*see* figure 3*A*). Numerous previous roentgenograms of the chest had not revealed this lesion, including the chest film

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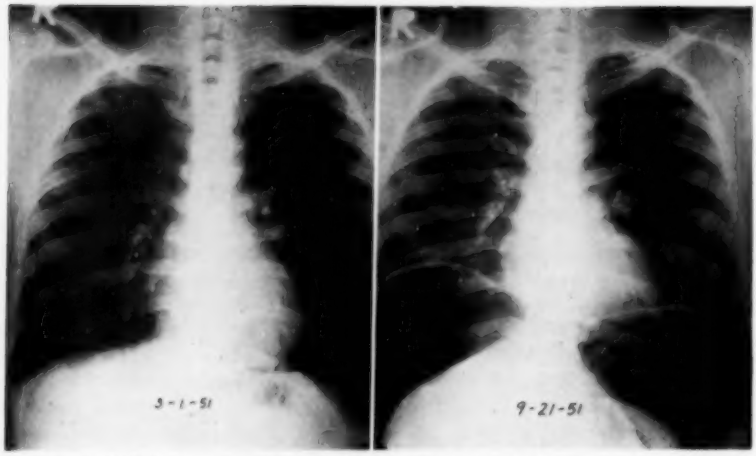

FIG. 1. (Left) Chest roentgenogram of March 1, 1951, before pneumoperitoneum.
FIG. 2 (Right) Chest roentgenogram of September 21, 1951, after institution of pneumoperitoneum.

of March 1, 1951 (figure 1), taken prior to any collapse therapy, and the chest roentgenogram of September 21, 1951 (figure 2), taken six months after the institution of pneumoperitoneum. The exact significance of this finding was not clear. The chest roentgenogram of May 22, 1952 (figure 3*B*) revealed that the previous minute lucency had now become an 8 cm. area of rarefaction. Since at this time the patient's sputum cultures again became positive for tubercle bacilli, it was believed that a cavity in the right lower lobe in the posterior sulcus between the diaphragm and the posterior chest wall was present. Because this huge rarefied area had developed while the patient was receiving streptomycin, some observers believed that this was not a cavity but a cyst. A chest film of October 14, 1952 (figure 3*C*) revealed the "cavity" to be slightly smaller, now measuring 6.4 cm. across, with the appearance of a fluid level. A right lateral film taken on that date (figure 4) revealed the cystic structure to measure 5.0 by 2.4 cm.

Operation: The patient underwent surgical exploration on October 31, 1952. On the posterior superior surface of the right diaphragm was a cystic structure with a very thin wall which contained gas. It was approximately 5 cm. in diameter and was not attached to the lung at any point, but was connected to the diaphragm by a stalk 1 cm. in diameter. This stalk was clamped and transected. In the center of the stalk, a perforation of the diaphragm through which air from the pneumoperitoneum bubbled could be seen. This defect in the diaphragm was approximately 1 mm. in size. It was believed that the "cyst" was formed by the herniation of peritoneum which had been pushed upward by the pneumoperitoneum through a defect in the right diaphragm with parietal pleura overlying it. This small defect in the diaphragm was closed with interrupted cotton sutures.

Examination of specimen: Grossly, the specimen (figure 6) consisted of a round, grayish-pink, cystic structure which measured 5 cm. in diameter with a thin wall. On section, the cyst contained gas and had an inner surface lined by a smooth membrane. Microscopic examination of the sections of the cyst revealed a wall composed of dense hyalinized connective tissue containing a few plasma cells and lymphocytes and many dilated vascular channels. *Both surfaces of the cyst wall appeared to be lined by mesothelium.* In many areas the mesothelial cells were multinucleated and resembled foreign-body giant cells.

The patient's gastric cultures had become negative for tubercle bacilli just prior to the resection of the diaphragmatic bleb and have remained so. His postoperative course was

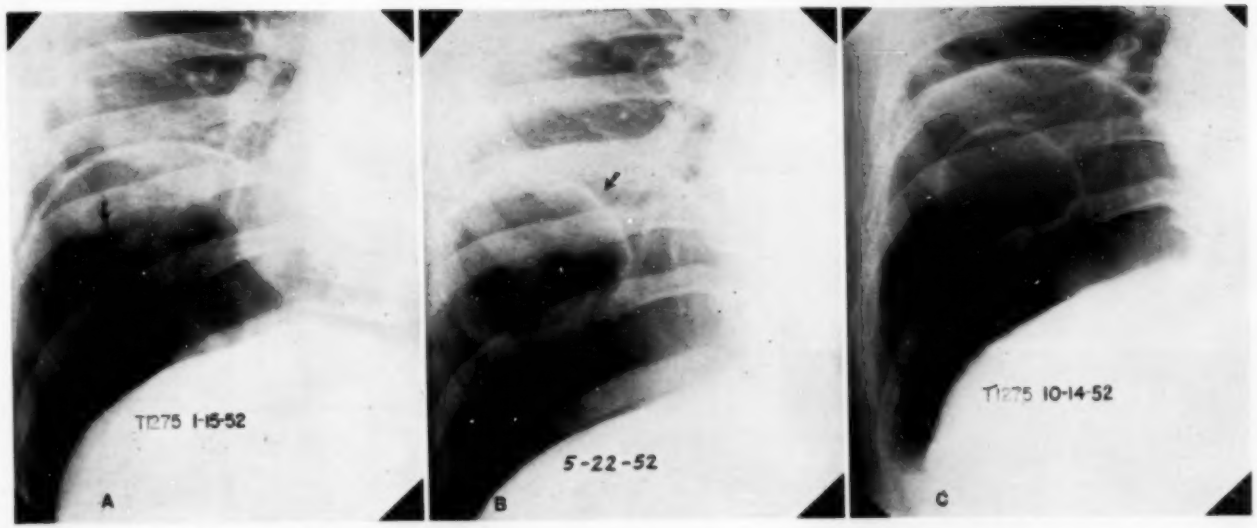

FIG. 3. Enlargement of right lower lung field of chest roentgenograms showing varying states of the bleb: *A*. January 15, 1952; *B*. May 22, 1952; *C*. October 14, 1952.

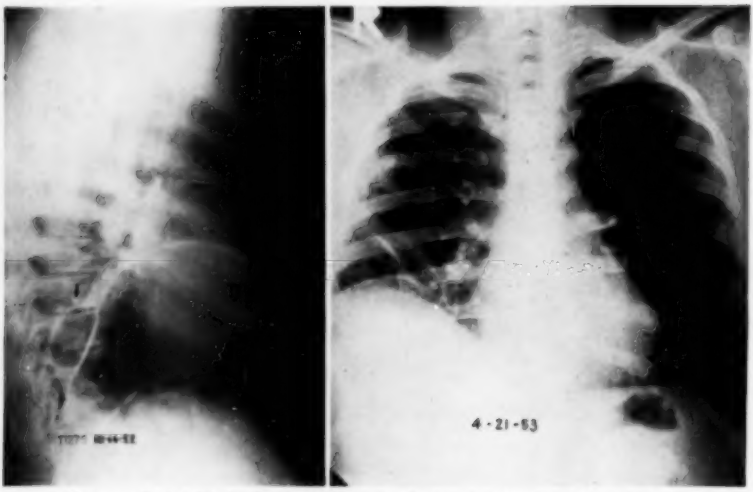

FIG. 4. (Left) Right lateral film revealing posterior location of bleb.
FIG. 5. (Right) Postoperative chest film.

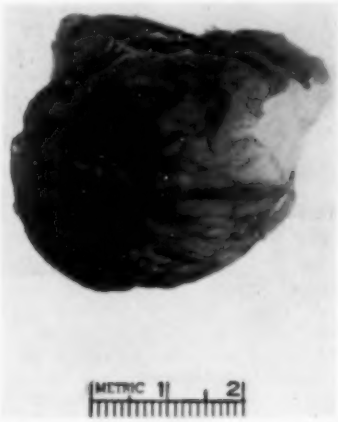

FIG. 6. Bleb reconstructed after surgical removal.

uneventful, and a chest film of April 21, 1953 (figure 5) revealed postoperative adhesions and elevation of the right diaphragm.

COMMENT

Diaphragmatic defects may be inflammatory, traumatic, degenerative, or congenital in origin. In the present case at thoracotomy, no supporting evidence for the presence of the first three causes was found. Congenital defects have been described posteriorly on both the right and left sides of the diaphragm. These are known as the pleuro-peritoneal hiatuses, or Bochdalek's foramina (figure 7). These defects are normally reinforced by the liver on the right, but in the pneumoperitoneum the liver and diaphragm are often sepa-

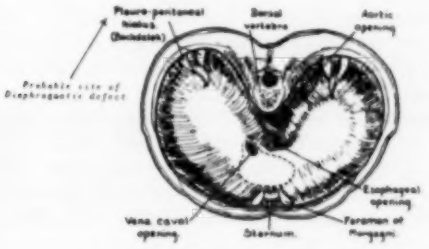

FIG. 7. Cross-section of diaphragm, revealing probable site of defect (*modified from Ritvo* [6]).

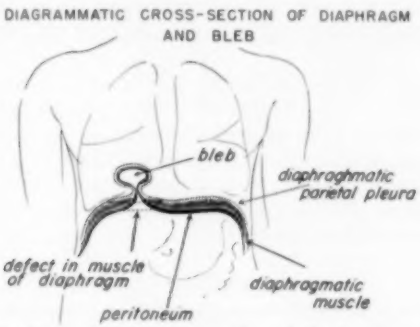

FIG. 8. Diagrammatic cross-section of diaphragm and bleb.

rated, subjecting these areas to the pressure of the intra-abdominal air present. Ross and Farber (2) have suggested that the small positive pressure of the artificial pneumoperitoneum is not in itself sufficient to cause a rupture of the diaphragm, but that this may occur when the patient, by straining at stool, coughing, or lifting heavy objects increases greatly the normal intra-abdominal pressure.

The posterior location of the bleb in the present case appears to point to the pleuro-peritoneal hiatus as the site of the defect. The bleb was on the right, and it is interesting to note that in all of the above-mentioned twenty-two cases (1–5) the spontaneous pneumothorax was on the right. It seems reasonable, therefore, to hypothesize the following chain of events: (*1*) a congenital defect in the posterior part of the diaphragm; (*2*) the induction of artificial pneumoperitoneum, with the subjection of the congenital defect to intraperitoneal air under positive pressure; (*3*) a ballooning of the peritoneum through the defect, forming a bleb of the overlying diaphragmatic parietal pleura (figure 8); (*4*) rupture of the pleuro-peritoneal sac, with concomitant leakage of the intra-abdominal air into the right pleural space, leading to right lung collapse, dyspnea, chest pain, and, rarely, sudden death.

During thoracoscopy, Laird (7) reported seeing blebs on the upper surface of the diaphragm in four patients who were receiving pneumothorax and pneumoperitoneum concurrently and who had had a previous right phrenic paralysis. Ross and Farber (2) mention a personal communication from Dr. J. Hallam Cope, who, while performing pneumonolysis on a patient who had had a spontaneous pneumothorax complicating his pneumoperitoneum therapy, observed through the thoracoscope a large bleb of the di-

aphragmatic pleura which varied in size with each respiration, enlarging whenever intra-abdominal pressure increased. This account appears to correspond with the roentgenographic finding in the present report, in which at different times the bleb appeared to be of different size.

Both Repa and Jacobson's case (5) and the one reported by Yannitelli and associates (3) showed roentgenographic findings of bleblike shadows on the pleural surface of the right diaphragm, as did the present case, strongly suggesting a similar etiology in the three cases. Since, in the case terminating fatally, blebs were demonstrated roentgenographically ante mortem, surgical removal of such blebs is indicated whenever they can be detected.

SUMMARY

Eventration of the peritoneum through a defect of the right diaphragm secondary to pneumoperitoneum is a rare complication of pneumoperitoneum therapy. In the case reported, the bleb was removed surgically before perforation occurred, and the patient is now living and well.

SUMARIO

Eventración Transdiafragmática del Peritoneo Secundaria al Neumoperitoneo

La eventración del peritoneo a través de una brecha del lado derecho del diafragma, secundaria al neumoperitoneo, constituye una rara complicación de la neumoperitoneoterapia. En este caso, se extirpó quirúrgicamente la ampolla antes de sobrevenir perforación, y el enfermo se encuentra hoy día vivo y sano.

RESUME

Eventration transdiaphragmatique du péritoine secondaire à la création d'un pneumopéritoine

L'éventration du pneumopéritoine à travers un défaut du diaphragme droit, à la suite d'un pneumopéritoine est une complication rare du pneumopéritoine thérapeutique. Dans ce cas, le sac a été excisé avant que la perforation ne se produise et le malade est actuellement vivant et en bonne santé.

Acknowledgments

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(3) Yannitelli, S. A., Woodruff, C. E., Mueller, E. E., and Howard, W. L.: Fatal tension pneumothorax resulting from diaphragmatic rupture in a patient receiving pneumoperitoneum, Am. Rev. Tuberc., 1949, *60*, 794.

(4) Wu, J. F., and Neptune, W. B.: Pneumothorax as a complication of pneumoperitoneum, Am. Rev. Tuberc., 1951, *63*, 710.

(5) Repa, J. J., and Jacobson, H. R.: Spontaneous pneumothorax, the result of a ruptured diaphragm complicating pneumoperitoneum, Am. Rev. Tuberc., 1951, *63*, 587.

(6) Ritvo, M.: Chest X-ray Diagnosis, Lea and Febiger, Philadelphia, 1951, p. 330.

(7) Laird, R.: Comments on total thoracoscopy, Tubercle, 1945, *26*, 149.

Notes

EFFECTS OF DECREASING DOSAGES OF CORTICOTROPIN UPON THE COURSE OF OCULAR TUBERCULOSIS IN THE RABBIT[1]

In continuing studies upon ocular tuberculosis in the rabbit, it has been reported that adrenocorticotropic hormone, in maximal dosage, altered deleteriously the course of the infection.[2] In amounts sufficient to increase both the weight and vitamin C content of the adrenal gland, administration of the hormone caused a worsening of the local disease, commonly was associated with its distant spread, and often resulted in the animal's death from tuberculous infection. This pernicious influence upon the animal's infection was associated with the development of acute tuberculous inflammation which had characteristics not unlike that seen in other acute bacterial infections. Caseation and localizing fibrosis were not observed as early in the course of the ocular disease as occurred in the untreated animal.

In a sense, this acute response could conceivably be of some advantage to the host. Under proper circumstances the acute inflammation might be capable of complete reversal, without residual difficult and permanent fibrotic disease. An effort was made, therefore, to obtain this advantage by manipulation of the dosage of adrenal hormone. Corticotropin was administered in an amount less than that which provides maximal adrenal stimulation and, to some, therapeutic amounts of streptomycin and isoniazid were also given. Ocular infection was established in the described fashion, and treatment was instituted within the next twenty-four hours. Fourteen rabbits were given corticotropin in parenteral doses less than 1 mg. per kg. per day; 7 animals received 0.5 mg. per kg. daily, 2 received 0.1 mg. per kg., and 5 were given combined therapy with isoniazid (5 mg. per kg. per day), streptomycin (20 mg. per kg. per day), and 0.5 mg. of corticotropin per kg. per day.

The results are summarized in table 1. The combined hormonal-antimicrobial therapy prevented advanced disease, and no distant lesions were found at autopsy. Although corticotropin was given in amounts sufficient to cause adrenal gland enlargement, the increased weight was less than that observed in animals given 1 mg. of corticotropin per kg. The amount of disease observed in the 5 rabbits never extended beyond the minimal stage, but in no instance was the lesion totally prevented. More importantly, the single tubercle persisted in each animal and its surrounding zone of inflammation was not significantly different from that seen in controls treated with streptomycin-isoniazid alone.[3] Complete resolution of the tuberculous lesion did not occur macroscopically.

One-tenth of a milligram of corticotropin per kilogram of body weight per day did not cause adrenal hypertrophy; ocular disease in the 2 animals was precisely that observed in the untreated controls. This dosage of corticotropin caused minimal increased adrenal gland weight.

It appears that combined adrenal hormone in less than maximally stimulating doses and streptomycin-isoniazid therapy in proved effective amounts does not provide the tuberculous animal a background of tuberculous inflammation which is capable of being totally resolved, or for that matter the protection needed to prevent fibrotic tuberculosis. It can also be concluded that adrenal hormone in these smaller doses is associated with lesser

[1] This investigation was supported by a grant from the Committee on Medical Research of the American Trudeau Society, medical section of the National Tuberculosis Association.

[2] BUNN, P. A., AND DROBECK, B.: Am. Rev. Tuberc., 1952, *66*, 175.

[3] BUNN, P. A., AND ROBINSON, F. O.: Am. Rev. Tuberc., 1954, *69*, 1016.

TABLE 1

EFFECT OF DECREASING DOSAGES OF CORTICOTROPIN UPON THE RABBIT WITH OCULAR TUBERCULOSIS

REGIMEN	NUMBER OF ANIMALS DEVELOPING OCULAR TUBERCULOSIS	NUMBER DEVELOPING ADVANCED EYE DISEASE	NUMBER WITH DISTANT LESIONS AT AUTOPSY	AVERAGE ADRENAL WEIGHT AT AUTOPSY [SINGLE GLAND]	AVERAGE WEIGHT OF ANIMAL AT AUTOPSY
				mg.	*kg.*
0.5 mg. per kg. per day corticotropin	7	7	4	160	3.03
0.5 mg. per kg. per day corticotropin and streptomycin-isoniazid	5	0	0	215	3.13
0.1 mg. per kg. per day corticotropin	2	2	2	70	3.20
Controls	4	4	3	51	3.34

local infection and fewer distant spreads of disease than is observed with larger amounts; the degree of deleterious alteration upon the ocular tuberculosis being, therefore, dependent upon dosage of the hormone.

It has been shown by many investigators that corticotropin fails to exert a deleterious effect upon tuberculosis in most body tissues in contrast to the situation with cortisone.[4, 5] The present observations in the rabbit eye represent a singular exception to this general body response, and the discrepancy requires explanation.

It is apparent from the present report that the degree of corticotropin's effect is directly proportional to total daily dosage of the hormone and that decreasing doses cause less general spread of the disease; but the deleterious hormonal effect is predictable and universal as far as the rabbit eye is concerned. Disease in the eye may not be, on the other hand, a representative tissue to study host-parasite relationships. It is possible that, despite consistency within the eye, tuberculous inflammation is altered by corticotropin in a different fashion elsewhere. This is not necessarily a unique experience. A similar discrepancy between host response to spirochetal infection in the eye and that after inoculation intratesticularly has been reported in rabbit syphilis.[6, 7] In this situation, although first inoculation of *Treponema pallidum* confers almost total protection against a second inoculation if sufficient time elapses between the inoculations, not all tissues share equally in being resistant, and the eye is one of these. It is possible to reinoculate successfully an eye of a rabbit previously infected with syphilis so that no absolute local immunity in the eye ever develops irrespective of where the first inoculation is given, intrascrotally or intraocularly.

It must be emphasized, therefore, that, although the observations made upon rabbit eye tuberculosis are consistent, the deleterious effects exerted upon its course by corticotropin need not be translated into suggesting that the hormone is harmful to the rabbit's and presumably any host's response to tuberculosis elsewhere. It is at this moment impossible to even intimate what mechanisms existing in the host, including the eye, are responsible for this discrepancy in response. It can be anticipated, however, that, with an explanation, body reaction to any tuberculous infection will become more clear. The differ-

[4] LEMAISTRE, C., AND TOMPSETT, R.: J. Exper. Med., 1952, *95*, 393.
[5] BACOS, J. M., AND SMITH, D. T.: Am. Rev. Tuberc., 1953, *67*, 201.
[6] BROWN, W. H., AND PEARCE, C. L.: J. Exper. Med., 1921, *34*, 167.
[7] CHESNEY, A. M.: Medicine, 1926, *5*, 463.

ence between the type of tuberculosis in the rabbit's eye and that in the lung and their respective different responses to corticotropin offer a fertile field for such a study.

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CYSTLIKE CAVITIES WITH ISONIAZID THERAPY IN PULMONARY TUBERCULOSIS

It has been observed commonly that antimicrobial therapy in pulmonary tuberculosis has produced no new mechanisms of healing; however, tuberculous lesions treated with isoniazid have assumed the roentgenographic appearance of cystlike cavities in enough cases to suggest a sharp increase in the incidence of that rare mode of cavity healing described by Pinner[1] and others[2] in the pre-drug era as "open healing." In these lesions "the cavum does not become obliterated but the cavity wall heals with an inner lining consisting of a smooth, clean layer of fibrous tissue," . . . free of granulations, necrotic and caseous material and free of bacilli . . . "uncertain in its differentiation from an emphysematous bleb."[3] Pinner records this process as occurring in "a highly selective minority" of cavity bearers, "who survive ten, twenty or more years by a kindly fate," and then it occurs "only in small cavities, and is not likely to be complete."

In 22 patients who received isoniazid therapy, sterile cystlike cavities replaced recognizable tuberculous disease at the site of earlier cavitary involvement. Particularly in Negroes, roentgenographic densities rapidly resolved, and large, empty, thin-walled air sacs, indistinguishable from cysts, developed. On serial roentgenograms, cystlike spaces gradually coalesced during a period of six months to a year into giant air sacs. Parenchyma of normal appearance was separated from a void by a faint shadow which might be cast by the thinnest of membranes.

This phenomenon, preceded by "conversion" of sputum and abeyance of symptoms, does not occur commonly. It has been observed in only 22 patients in an institution with 614 beds since the use of isoniazid was initiated in June, 1952. It is interesting to note that 20 of these were Negro patients in a sanatorium in which the census is about equally divided as to race. This dramatic drug response was not related to type or chronicity of disease and was unaffected by the presence of pneumoperitoneum. It was observed when isoniazid was given alone or in combination with streptomycin, dihydrostreptomycin, or para-aminosalicylic acid.

On 4 surgical specimens from this series, resected six months to one year after sputum "conversion," a histologic diagnosis of tuberculous disease could not be made. The walls of cystlike cavities, which had increased in size on isoniazid therapy, consisted of loose to dense fibrous tissue with collagen fibers parallel to the surface. The cavities were not lined with epithelium, although grossly their inner surfaces were smooth and glistening. In the writers' experience, "open healing" of this degree and incidence is unprecedented with other antimicrobial agents. In earlier clinical studies with streptomycin and dihydrostreptomycin, however, the histopathology of an apparently similar though incomplete process was reported after shorter courses of drug by Flory, Hobson, Muschenheim, and their associates[2-5]. Auerbach[6] concluded that "open healing" in streptomycin-treated cases

[1] Pinner, M.: Pulmonary Tuberculosis in the Adult, Charles C Thomas, Springfield, Illinois, 1945, pp. 73, 76.

[2] Huebschmann, P.: Pathologische Anatomie der Tuberkulose, Julius Springer, Berlin, 1928.

[3] Flory, C. M., Correll, J. W., Kidd, J. G., Stevenson, L. D., Alvord, E. C., Jr., McDermott, W., and Muschenheim, C.: Am. Rev. Tuberc., 1948, *58*, 421 (Case 6, footnote 5).

[4] Hobson, L. B., Tompsett, R., Muschenheim, C., and McDermott, W.: Am. Rev. Tuberc., 1948, *58*, 501 (Case 4).

[5] Muschenheim, C., McDermott, W., Hadley, S. J., Hull-Smith, H., and Tracy, A. L.: Ann. Int. Med., 1947, *27*, 989.

[6] Auerbach, O., Katz, H. and Small, M. J.: Am. Rev. Tuberc., 1953, *67*, 173, 194–195.

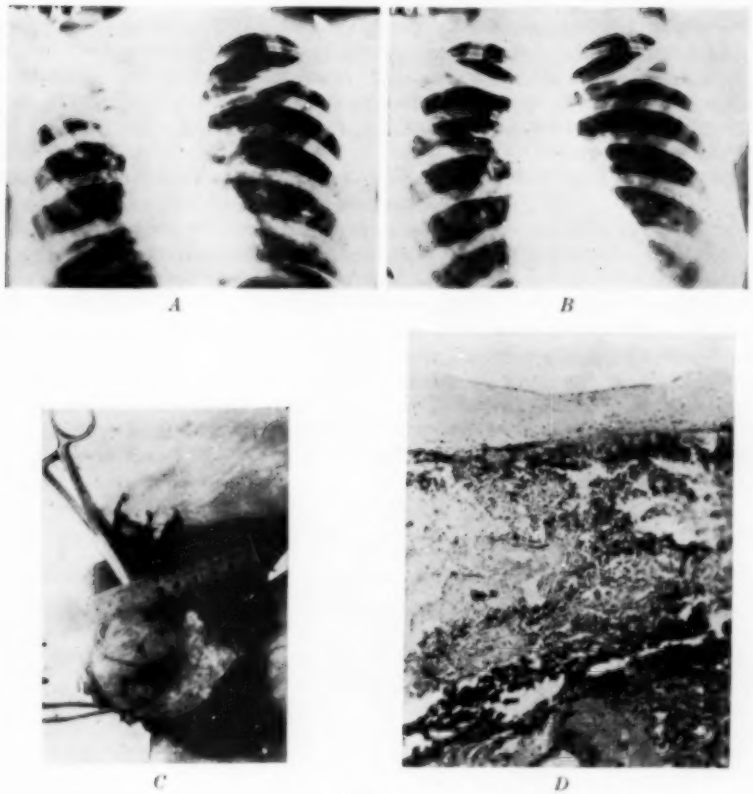

FIG. 1

A. Roentgenogram made on May 16, 1952, before isoniazid therapy (L. T., 23-year-old Negro female).

B. Roentgenogram made on July 20, 1953, before right upper lobectomy.

C. Resected specimen, showing interior of cystlike cavity.

D. Photomicrograph of typical section of wall of cystlike cavity.

was characterized by re-epithelization of varied extent initiated at the bronchocavitary junction and often extending far around the inner cavity wall. Such cavities greatly diminished in size, and their contents tended to become inspissated about viable organisms. Huebschmann[2] never observed epithelization of an "open healed cavity" prior to antimicrobial therapy, but did not doubt that it might occur. Pinner stated, "So-called epithelized cavities are difficult, or at times impossible to distinguish from small bronchiectatic cavities." Perhaps it is significant that epithelium was not present in sections from cavity walls in these resected specimens (figure 1). Neither were the "necrotic residuals" of D'Esopo and his associates[7] apparent.

[7] D'ESOPO, N. D., BERNSTEIN, S., LEE, W. F., DECKER, A. M., AND STEENKEN, W. JR.: Tr. Eleventh Conference on the Chemotherapy of Tuberculosis, January 17 to 20, 1952, St. Louis, Missouri.

The process described appears to have been "open healing." A knowledge of this process and serial roentgenograms are necessary to distinguish these camouflaged cavities from true cysts or the emphysematous blebs seen occasionally in healed tuberculous disease. Evaluation of patients under isoniazid therapy is further complicated by the increasing incidence of these sterile cystlike cavities because their subsequent course has been observed to be variable:

1. They may enlarge, even to giant size, occupying many times the area of original disease.
2. They may close after temporary increase in size.
3. They may revert to typical tuberculous cavities, with a recurrence of symptoms and a return of demonstrable tubercle bacilli in the sputum.

The degree to which the phthisiologist may trust "open healing" which has proceeded relatively rapidly on antimicrobial therapy poses a new problem. The "therapeutic target point"[8] (stable disease on roentgenograms, cavity closure, and negative bacteriology) has been reached except for cavity closure. Particularly in Negro patients, the potential hazard of these sterile cystlike cavities as disease residuals must be evaluated and clarified.

THE NORTH CAROLINA SANATORIUM
McCAIN, NORTH CAROLINA

LYNN JOHNSEN
WILLARD C. HEWITT

October 21, 1953

Acknowledgment

Grateful acknowledgment is made to the Director of Laboratories and Research, The Gravely Sanatorium, Chapel Hill, North Carolina, H. Mac Vandiviere, who prepared the photomicrograph and reproductions of the surgical specimen and roentgenograms.

[8] D'ESOPO, N. D.: J.A.M.A., 1954, *154*, 56.

TUBERCULIN-TESTING STUDIES IN NEW YORK CITY

Information regarding the prevalence of positive tuberculin reactions in New York City according to age is given in table 1. The results were obtained during 1950–1952 in studies conducted by the Department of Health of the City of New York through testing of persons in a number of groups which overlapped to some extent in their age limits. None of the groups can be considered representative of the population of the city, or of any of the elements of that population, because the composition of each is biased in one or more ways. Furthermore, for the sake of simplicity in presentation, no breakdowns by sex or color are given although these are available.

The testing material employed in all instances was Old Tuberculin. This was administered to the members of the first group in patch tests. The members of the other groups were given intradermal tests with 0.1 mg. of OT. No further tests were given to nonreactors in any of the groups.

The first group consisted of well children attending six of the Child Health Stations of the Department of Health. Very few were tuberculosis contacts, and most of them were less than two years old. These facts may account for the low percentage of positive reactors,

TABLE 1

PERCENTAGE OF POSITIVE REACTORS TO TUBERCULIN BY AGE, NEW YORK CITY, 1950–1952

GROUP TESTED	AGE CATEGORIES	NUMBER TESTED	PER CENT POSITIVE
Child Health Station patients	0–4 years	3,300	4.3
High school students	13 years	1,098	5.7
	14 years	4,237	8.4
	15 years	6,623	11.8
	16 years	6,202	14.4
	17 years	3,488	19.4
	13–17 years	21,648	12.8
Chest clinic patients	0–4 years	460	11.7
	5–9 years	524	16.0
	10–14 years	347	28.8
	15–19 years	400	26.8
	20–24 years	593	43.9
	25–34 years	157	56.0
	35–44 years	719	71.5
	45–54 years	455	81.2
	55–64 years	283	80.6
	65 years and older	136	69.1
Residents of homes for aged	65–74 years	530	60.8
	75–84 years	829	55.9
	85 years and older	269	49.5
	65 years and older	1,628	56.4

although the proportion of non-white children was considerably higher than in the general population of the city. The result obtained may be compared with that in the corresponding age category among clinic patients, in whom the proportion of contacts was high.

Those tested in the second group were students attending fifteen of the city high schools. There were significantly more girls than boys in the group, but the color composition was not too divergent from that of the city population. The percentage of positive reactors in a roughly corresponding age class of clinic patients (15–19 years) was markedly higher. However, in the latter case, the proportion of non-white persons and contacts was distinctly greater.

The third group was composed of patients admitted to one of the Health Department District Chest Clinics for any reason other than the presence of tuberculosis. There were naturally more contacts and persons with symptoms of illness among them. Furthermore, there were significantly higher proportions of persons in the 15 to 34 year age groups and in the non-white category than in the district at large.

Tuberculin tests given to the residents of one municipal and three denominational homes for the aged provided the data for the fourth group. These persons were all 65 years and older, almost exclusively white, and preponderantly of Central and Eastern European origin. Moreover, there were proportionally more persons in the 75 to 84 year and 85 year and older categories among them than among those 65 years and older in the general population. A lower percentage of positive reactors was found than in the corresponding age category of clinic patients. This is probably due to differences in age and color composition and presumably a lower proportion of contacts than in the clinic group. Most striking was the low tuberculin reaction rate in this older population and its decrease as the ages of its individual members increased. Possible explanations for this are waning of tuberculin sensitivity concomitant with lack of opportunity for reinfection in an institutional environment and changes in the sensitivity of the skin in older persons.

These data on the results of tuberculin tests in certain segments of the population of New York City are submitted as a basis for comparison with the findings in similar groups and in future studies.

Department of Health
New York City

February 18, 1954

Arthur B. Robins
H. Abeles
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H. Konterwitz
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Correspondence

GROWTH OF TUBERCLE BACILLI IN MONOCYTES FROM NORMAL AND VACCINATED RABBITS

To the Editor of The American Review of Tuberculosis:

Dr. Mackaness notes in his paper "The Growth of Tubercle Bacilli in Monocytes from Normal and Vaccinated Rabbits" (Am. Rev. Tuberc., 1954, *69*, 495) that, in 1942, it was shown that washed phagocytes derived from immunized rabbits which had ingested tubercle bacilli and carbon particles *in vitro* in the presence of normal rabbit serum, and which had subsequently been implanted into the anterior chamber of one eye of a normal albino rabbit, inhibited the growth of tubercle bacilli to a much greater degree than cells derived from normal animals similarly parasitized and incubated in the anterior chamber of the opposite eye of the same rabbit. The observations are not contested by Dr. Mackaness, as they were based, not only on direct histologic observations, but also on quantitative cultural studies. However, he proposes an alternative interpretation for the data. He imputes the observed bacteriostasis in the carbon-laden cells derived from the immunized donor to the transfer of allergy to the chamber implanted with these "immune cells." He cites the well-known and thoroughly established work of Chase on the transfer of allergic sensitivity to normal animals by the introduction of cells derived from a sensitized donor. He further states, and with good reason, that there is evidence that such transferred allergy may be confined to the chamber implanted with "immune" cells and that, therefore, the normal cells implanted in the opposite anterior chamber of the same rabbit grow in a nonallergic environment and hence do not inhibit the growth of the bacilli.

Now, just what does Dr. Mackaness mean by allergic sensitivity? Does he mean that the anterior chamber implanted with "immune" cells containing tubercle bacilli is the site of increased inflammation which is responsible for the bacteriostasis? Surely, this is hardly tenable. It has been definitely shown by Raffel that one can induce true allergic sensitivity in normal animals by treating them with the combined "wax" and protein of the tubercle bacillus. However, this allergy does not confer any protection against the multiplication of the bacilli. Therefore, Dr. Mackaness cannot attribute the bacteriostasis to this phase of allergy. Furthermore, as Dr. Mackaness himself remarks, there was much more inflammation in the anterior chamber implanted with normal cells than in that implanted with "immune" cells. This is simply due to the observed greater multiplication of the bacilli in the normal cells and, therefore, to the greater chemotaxis exerted by the multiplying bacilli in that chamber.

Dr. Mackaness calls attention to the epithelioid character of the cells of the chamber implanted with "immune" cells and considers it a reaction of reinfection and different from the lesion in the anterior chamber implanted with normal cells. But as the "immune" cells destroy the tubercle bacilli, epithelioid cell formation is a direct consequence. We have shown during many years under the most diverse conditions of native and acquired resistance to tuberculosis that epithelioid cell transformation of mononuclears is always associated with the intracellular destruction of tubercle bacilli. Dr. Mackaness implies that these epithelioid cells may even be derived from the host rather than from the implanted cells, although he admits that these cells still contain the carbon particles which were in these phagocytes before implantation.

Dr. Mackaness is not quite clear about this, but he may consider that, not only is

allergic sensitivity transferred by the "immune" cells to the tissues of the implanted chamber, but also with it is transferred an increased capacity to inhibit the growth of the bacilli within the mononuclears derived from the host. Certainly, the data available at present do not warrant such a far-reaching conclusion. Until such a premise is established, our interpretation is the simplest and most direct; namely, that the cells themselves of the immunized animal retain their increased capacity to inhibit the growth of tubercle bacilli in their cytoplasm even when transferred to a normal host. Indeed, in our paper we drew an analogy between the retention of bacteriostasis by the "immune" cells in a nonimmune environment and the retention of allergic sensitivity by cells derived from sensitized animals when grown in tissue culture over successive transplants. This was demonstrated by Moen.

Dr. Mackaness' criticism of our studies, that the seeding of the two cell types with tubercle bacilli was not the same, is, in the first place, not quite exact. Reference to table 3 of our paper of 1942 shows that the number of bacilli present in the normal and "immune" cells before implantation, while not identical, were, nevertheless, quite close. Furthermore, this stricture has no direct relevance, for our conclusions are based, not on the mere greater numbers of bacilli present in the cells derived from the normal animal two weeks after implantation, but on the *relative* increase of the microorganism in the respective cells at this time as compared with the number of bacilli present in the original inoculum implanted in each eye.

It would seem to me that all Dr. Mackaness is entitled to conclude from present knowledge is that by his *in vitro* methods he failed to show what has been demonstrated by *in vivo* procedures. Furthermore, Dr. Suter has confirmed our conclusions by an alternate tissue culture method. I hope Dr. Suter will adequately answer Dr. Mackaness' objections to the procedures used by him.

Respectfully yours,

Max B. Lurie

The Henry Phipps Institute
of the University of Pennsylvania
Philadelphia, Pennsylvania

March 22, 1954

To the Editor of The American Review of Tuberculosis:

In two papers in the April issue of the *Review* (Am. Rev. Tuberc., 1954, *69*, 479, 495), Mackaness reports findings which are at variance with our own results obtained when studying intracellular multiplication of tubercle bacilli in macrophages from experimental animals. The differences concern the rate of multiplication of strains of varying degrees of virulence within macrophages from the same species as well as the inhibitory power exerted upon intracellular tubercle bacilli by macrophages derived from animals vaccinated with BCG (Suter, E.: J. Exper. Med., 1952, *96*, 137; 1953, *97*, 235). In view of these discrepancies, some of the factors which might possibly alter the interaction between macrophages and tubercle bacilli will be analyzed, and their significance for the above mentioned differences will be discussed.

1. Mackaness' results indicate that the rate of multiplication of different strains of tubercle bacilli within macrophages from rabbits corresponds to the degree of virulence or attenuation of the strain, whereas, in our own experiments, virulent as well as attenuated strains of tubercle bacilli multiplied at a similar rate within macrophages derived from guinea pigs. No direct comparative experiments had been done with rabbit

macrophages, but it was found in independent experiments that a virulent and an attenuated strain did multiply intracellularly; but a comparison of rates could not be made. The most obvious difference between virulent and attenuated tubercle bacilli was found to be the damaging effect of the accumulating bacilli on the host cells. Thus, a virulent strain would destroy the cells when the number of the bacilli had reached more than 10 or 15, whereas the macrophages could contain large numbers of attenuated bacilli without apparent damage. Doubt is expressed by Mackaness of the validity of quantitative evaluation of intracellular multiplication on the grounds that the changes observed could be due to redistribution rather than to multiplication.

Originally, we were doubtful, too, but the following findings convinced us that the changes were due to intracellular multiplication: (*1*) The percentage of macrophages containing bacilli remained relatively constant throughout the period of cultivation unless the cells were destroyed by the increasing number of bacilli, as was the case with virulent organisms after the fifth day of cultivation; (*2*) infection with dead bacilli did not result in any change of the number of bacilli per infected macrophages; and (*3*) complete inhibition by 80 to 100 γ of streptomycin per ml. was reflected also by a constant number of stainable bacilli present in the cells. If virulent organisms did multiply at a faster rate than the attenuated ones, the difference could not be observed within the first four days of cultivation, during which very little damage was done to the cells.

Mackaness expresses the opinion that the spindle-cells appearing in macrophage cultures were fibroblasts or serosal cells rather than transformed macrophages. However, there is good evidence that blood monocytes do transform into spindle-shaped cells (TIMOFEJEWSKY, A. D., AND BENEWOLENSKAJA, S. W.: Virchows' Arch. f. path. Anat., 1928, *268*, 629; EBERT R. H., AND FLOREY, H. W.: Brit. J. Exper. Path., 1939, *20*, 342), and Fawcett states that "these marked variations in the appearance of a single cell type growing *in vitro* . . . demonstrate the inadequacy of cell-shape as a criterion for the identification of cell types" (WEISS, L. P., AND FAWCETT, D. W.: J. Histochem. & Cytochem., 1953, *1*, 47).

2. Mackaness' findings do not confirm our results on the growth inhibitory property exerted on intracellular tubercle bacilli by macrophages from animals vaccinated with BCG. The question arises what factors could influence the interaction between cells from vaccinated animals and tubercle bacilli. Observations made in the last year indicate that there are several factors which might possibly explain the differences. The number of tubercle bacilli present in the infected macrophages at the beginning of the cultivation period is of great importance for the outcome of the experiment. If the cells are infected with large numbers of tubercle bacilli, inhibition of multiplication is almost negligible. According to the figures given by Mackaness, his cultures were much more heavily infected than those in our own experiments. The percentage of cells infected ranged between 64 and 84, whereas the range was between 7 and 12 in our experiments. This results in an average number of about 4 to 5 bacilli per cell of the total population, which is ten times higher than in our cultures. That the number of bacilli of reinfection is an important factor in the outcome of the infection is indicated by results obtained from animal experiments as well as from clinical observations. In addition, the degree of hypersensitivity of the animals from which macrophages are taken seems to influence the inhibitory power of the cells. The vaccination procedure described by Mackaness consists of two injections of tubercle bacilli. Whether the second injection increases significantly the degree of hypersensitivity is not known, but it might possibly influence the reactivity of the cells to tuberculoprotein. More data are required to quantitate the influence of hypersensitivity on the interaction between macrophages and tubercle bacilli, and experiments aimed at such a clarification are in progress.

Finally, there is a difference of the technique employed which might be of importance. Mackaness was using paraffin oil to obtain peritoneal exudates, whereas glycogen was used in our experiments. Paraffin is known to alter some of the pathogenic effects of tubercle bacilli, and it is conceivable that macrophages containing even traces of the oil may provide a different environment for the tubercle bacillus than cells without it. But comparative experiments have not been done.

It should be mentioned that our own results on the inhibitory property of streptomycin and isoniazid on intracellular tubercle bacilli are in complete agreement with results obtained by Mackaness.

Sincerely yours,

EMANUEL SUTER

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March 19, 1954

A PROPOSED MODE OF ACTION FOR ISONIAZID IN THE TUBERCLE BACILLUS AND OTHER BIOLOGICAL SYSTEMS

To the Editor of The American Review of Tuberculosis:

Snell's postulated metal-pyridoxal phosphate-enzyme-substrate complex,[1] which is shown as a model for transamination reactions, seems to offer a very important clue to the mode of action of isoniazid. In this complex it might be assumed that cation such as Cu^{++}, Fe^{+++} or Al^{+++} is the effective metal cofactor involved in transamination (or any other reaction involving B_6, since it appears that a similar mechanism of action is involved in decarboxylation, dehydration, desulfhydration, racemization, tryptophane synthesis and hydrolysis, et cetera) since Metzler, Snell, and others have caused many of these typical B_6 utilizing reactions to take place nonenzymatically when pyridoxal, substrate, and either Cu^{++}, Fe^{+++}, or Al^{+++} are mixed under the proper conditions. Snell believes that the "common feature of these reactions lies in formation of a Schiff base between pyridoxal and amino acid, stabilized by chelation with a metal ion as indicated in figure 7 [of this review] and resulting in an activation of the amino acid residue so that it may undergo any of a variety of reactions in groupings immediately surrounding the carbon atom. The predominant nature and rate of these reactions is determined by the structure of the amino acid. It appears probable that metal ions will also prove essential for the analogous enzymatic reactions."

Fallab and Erlenmeyer have found that two moles of isoniazid form a chelate complex with one mole of Cu^{++} having a stability constant, determined spectrophotometrically, in the range of that characterizing a Cu 8-hydroxyquinoline complex.[2] 8-Hydroxyquinoline is known to form very stable chelate complexes with Cu^{++}, Fe^{+++}, and Al^{+++} under proper conditions. 8-Hydroxyquinoline is also known to be toxic to bacteria.

A hypothesis can be formulated to the effect that isoniazid, being a very strong complexing reagent, effective in very small concentrations under certain conditions, intracellularly chelates the essential metal cations in the critical enzyme systems of the bacteria which directly involve metal-pyridoxal phosphate-enzyme-substrate complexes.

[1] SNELL, E. E.: Physiol. Rev., 1953, *33*, 509.
[2] FALLAB, S., AND ERLENMEYER, H.: Helvet. chim. acta, 1953, *36*, 6.

Following the law of mass action any one of the four constituents (substrate, B_6, metal, or apoenzyme) of this enzyme complex might reverse, although competitively, the inhibiting effect of isoniazid in the cell. For example, with respect to substrate reversal of inhibition, Cedrangolo and associates found that glutamic acid is able to decrease the toxic effects of isoniazid in rats and rabbits.[3] With respect to coenzyme reversal of inhibition, Yoneda and associates have found that pyridoxal competitively reverses the inhibiting action of isoniazid on the tryptophane-splitting enzyme and arginine decarboxylase in *Escherichia coli*;[4] Pope found that B_6 antagonizes the action of isoniazid in Tween 80[5] medium without albumin after five hours' incubation.[6] With respect to ionic reversal of inhibition, Pansy and associates have found that Fe^{+++} at a pH of 9 in Dubos liquid medium prevents isoniazid inhibition of tubercle bacilli (at this pH, Fe^{+++} is probably most strongly bound by isoniazid, which, as is known, is an acid).[7] Possibly the saturation of all available bonds of isoniazid by Fe^{+++} occurs and enough ions remain to function effectively in the B_6-enzyme complex. With respect to apoenzyme reversal of inhibition, biotin is known to reverse isoniazid's toxic action, at least in the case of *Aerobacter aerogenes*.[8] This vitamin is considered to be involved in the synthesis of an apoenzyme or coenzyme involved in amino acid decarboxylation and the synthesis of unsaturated fatty acids. This effect may be due to an involvement in the synthesis of the apoenzyme of this complex.

The essential chelating group seems to be the —CO—NH—NH_2 part of the molecule. It is interesting to note that caprohydrazide, among other hydrazides, has antituberculous activity and contains this substituent group. Tubercle bacilli possessing resistance to this drug are also resistant to isoniazid.[9]

Vitamin B_6 has been known for some time to be involved in the synthesis of unsaturated fatty acids, which may be why in some cases isoniazid resistance involves a loss of acid-fastness.

Because of the rapid depressant action of isoniazid on the *in vitro* respiration of the tubercle bacillus, isoniazid may chelate Fe^{+++} bound by the cytochromes of that organism, since (*1*) certain isoniazid-resistant tubercle bacilli require hemin for growth, (*2*) hemin antagonizes isoniazid inhibition in isoniazid-sensitive organisms, and (*3*) as indicated above, Fe^{+++} at pH 9 in Dubos medium prevents isoniazid inhibition of tubercle bacilli.

Sincerely yours,
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(Graduate Student)

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February 24, 1954

[3] CEDRANGOLO, F., GIOIA, A., AND BAGNULO, R.: Enzymologia, 1953, *16*, 41.

[4] YONEDA, M., KATO, N., AND OLAJIMA, M.: Nature, 1952, *170*, 803.

[5] Tween 80 is the proprietary name for the polyoxyethylene derivative of Sorbitan monooleate, obtainable from the Atlas Powder Co., Wilmington, Delaware.

[6] POPE, H.: Am. Rev. Tuberc., 1953, *68*, 938.

[7] PANSY, F. E., KOERBER, W. L., STANDER, H., AND DONOVICK, R.: Am. Rev. Tuberc., 1953, *68*, 284.

[8] PETILLO, R. F., AND FOSTER, J. W.: J. Bact., 1954, *67*, 53.

[9] DIMARCO, A.: Antibiotics & Chemotherapy, 1953, *3*, 807.

Books

THE EFFECT OF ACTH AND CORTISONE UPON INFECTION AND RESISTANCE. Edited by Gregory Shwartzman. Symposium held at the New York Academy of Medicine, March 27-28, 1952. Pp. 204, with illustrations, Columbia University Press, New York, 1953, price, $5.50.

This symposium on the effect of corticotropin and cortisone upon infection and resistance has brought together under one cover a vast amount of clinical and experimental data. The data are often incomplete and the conclusions tentative.

In Frank L. Engel's discussion of the role of the adrenal cortex in intermediate metabolism, it was emphasized that the action of hormones is strictly regulatory since no single metabolic activity is either initiated, prevented, or even dependent upon hormones. And it has not been possible, as yet, to demonstrate any meaningful connection between known metabolic effects of the adrenal hormones and their therapeutic effectiveness.

The influence of adrenalectomy and cortisone treatment of certain enzymatic reactions in the rat was discussed by W. W. Umbreit. Umbreit concluded that the problem was difficult since a specific hormone treatment may have one effect upon an enzyme in one tissue, but another effect on the same enzyme in another tissue. Furthermore, a given enzyme may be under the control of one steroid hormone in one tissue, but under another hormone in a different tissue.

The effect of corticosteroids upon lymphoid tissue was reviewed by William E. Ehrich and Joseph Seifter. There is a rapid reduction in the number of lymphocytes following both corticotropin and cortisone treatment with a corresponding atrophy of thymus, lymph node, and other lymphoid tissues. The lysis of plasma cells can be demonstrated but is more difficult to measure.

The effect of cortisone upon repair processes in dense and loose connective tissue was presented by Charles Ragan and his associates. Cortisone delays the rate of time of repair and can be connected roughly with the amount of hormone administered. However, smaller doses produced greater changes in animals with poor nutrition, and animals of different species require different amounts of the hormone. Local applications of the hormone give results similar to systemic administration. The cellular effect seems to be exerted on the precursor of the fibroblast, since healing occurs when fibroblasts and new blood vessels appear.

A discussion of adrenal hormones and the development of antibody and hypersensitivity was presented by Edward E. Fischel. The amount of pneumococcal antibody nitrogen in the serum of rabbits was less in the animals treated with cortisone or corticotropin when measured after a nine- to fourteen-day period. But passively transferred antibody is not metabolized more rapidly by cortisone-treated animals. Pretreatment with cortisone did reduce the amount of antibodies produced by a second stimulating dose of antigen. The anaphylaxis and the Arthus types of antigen-antibody reactions are not inhibited by cortisone or corticotropin, probably because the antibodies were preformed and passively transferred. The tuberculin reaction in man and animal is reduced in severity by treatment with either corticotropin or cortisone, but the effect apparently results from an altered skin reactivity rather than an interference with an allergic reaction per se. Corticotropin and cortisone fail to suppress the immediate type of skin reaction to pollen antigen, and yet clinical evidence of improvement in asthma or hayfever can be observed in the same patient. Apparently, cortisone does not inhibit the union

of antigen and antibody or the resulting sensitization but may inhibit in a nonspecific manner the expected inflammatory reactions.

A. McGehee Harvey, Lawrence E. Shulman, and Edith H. Schoenrich reported their observations on the effect of corticotropin and cortisone on the allergic diseases such as urticaria, hay fever, asthma, purpura, and arthritis.

Herbert C. Stoerk found that cortisone depressed both the inherited and acquired resistance of rats to tumor grafts.

Lewis Thomas observed that cortisone and corticotropin reduced the amount of local inflammation following the intracutaneous injection of streptococci into rabbits but accelerated the invasion of the bloodstream and the death of the animal. It should be noted that large doses of the hormone were used: 5 mg. of cortisone per kg. and 20 mg. of corticotropin per kg. each day. Large doses of penicillin, if given early in the experiment, would protect the animal from fatal infection, but desoxycorticosterone, mineral salts, and pituitary somatotropic hormone had no beneficial effects.

Lewis could not prevent either the local or generalized Shwartzman reaction with 25 mg. or more of cortisone per kg. or with 40 mg. of corticotropin per kg. These observations are in conflict with those of Shwartzman, who used much smaller doses and a different interval of dosing.

Edward H. Kass, Quentin M. Geinman, and Maxwell Finland reported that the symptoms of pneumococcal pneumonia could be controlled with corticotropin, but positive blood cultures persisted. Antibodies were eventually developed and the patients recovered spontaneously. Mice which were not protected by corticotropin and cortisone showed a decreased antibody production and an increase in death rate as compared with the control mice. Growth homone did not inhibit the deleterious effect of the cortisone. Influenza A infection in adult mice was made worse by cortisone but not by corticotropin, but in neither was there an appreciably altered rate of multiplication of the virus. Rodent malaria, caused by *P. berghei*, which is usually a mild disease, becomes a highly fatal disease if the rats are given cortisone.

Gregory Shwartzman and Stanley M. Aronson reported their studies of poliomyelitis in the Syrian golden hamster. A single injection of 2 mg. of cortisone increased the mortality from 24.6 per cent to 77.8 to 100 per cent. In contrast, the injection of two doses of 10 mg. of corticotropin in gelatin during the twenty-four hours before infection did not increase the mortality rate.

Abner Wolf, Elvin A. Kabat, and associates, during some other studies, discovered that their experimental *Macaccus rhesus* monkeys were harboring a trypanosoma (probably *T. cruzi*). Twenty-two of the 59 monkeys which were treated with cortisone died with the typical lesions of trypanosomiases. None of the 20 controls died of this disease.

Thomas B. Turner and David H. Hollander studied the effect of cortisone on experimental syphilitic dermal lesions in rabbits. The amount of induration about the lesion was reduced, while at the same time there was an enormously accelerated multiplication of treponemae and a marked increase in the accompanying mucoid material. After the withdrawal of the cortisone, there was a rebound reaction, with a rapid increase in the size of the lesion and the amount of induration. Eventually, there was a reduction in the size of the lesion and a reduction in the number of treponemae. Generalized syphilitic lesions occurred in a much higher proportion of the cortisone-treated animals than in untreated controls.

Max B. Lurie and his associates reported on their studies in which rabbits of known genetic stock and degrees of resistance were treated with cortisone after being infected with the human type of tubercle bacillus. The rabbit received known numbers of tubercle

bacilli by the inhalation method. Small doses of cortisone were employed; 2 mg. per kg. every other day or on an average of 1 mg. per kg. per day. This dose was sufficient to reduce the lymphocyte count in a statistically significant manner; reduce the severity of the tuberculin test; reduce the capillary fragility of the skin; and reduce slightly the hemagglutinin titers. The cortisone was continued for thirty-four to thirty-eight days. Animals sacrificed at this time showed marked atrophy of the spleen, adrenals, and the male gonads. The ovaries were not affected. Three to four times more tubercles were found in the lungs of the cortisone-treated animals than in the controls. But the individual lesions were smaller, with less involvement of the regional lymph nodes. The monocytes in the lesions were filled with tubercle bacilli far in excess of anything seen in the controls. When the cortisone was stopped, the disease became rapidly progressive, with the development of massive pulmonary disease, hematogenous dissemination, and death of the susceptible rabbits. The resistant rabbits developed large pulmonary cavities. During the same time the untreated susceptible rabbits were reducing the extent of the disease and the resistant rabbits were healing their lesions. Cortisone seems to reduce the capacity of the macrophages to digest tubercle bacilli rather than stimulate the growth of this organism. Other studies by the same authors indicate that corticotropin in small doses does not have a deleterious effect on experimental tuberculosis in rabbits.

DAVID T. SMITH
Durham, North Carolina

COMMUNICABLE DISEASES. A Textbook for Nurses. Seventh Edition. By Albert G. Bower and Edith B. Pilant. Pp. 640, W. B. Saunders Company, Philadelphia and London, 1953, Price, $5.50.

Dr. Bower's and Miss Pilant's revised book on communicable diseases should be most useful to nurses as they prepare for positions in the outlying areas of this country and throughout the world. There are initial chapters on terminology and on basic medical aseptic technique as well as a helpful chapter on nursing of communicable diseases in the home and on control of communicable disease.

An appealing aspect of the book is its inclusiveness; it contains in a practical and handy form enough of the historical background as well as a thoughtful summary of medical management to make referral to more lengthy medical texts seldom necessary. Nursing care has been integrated in each chapter in a harmonious fashion with the medical content which nurses need to know in order to care for the patient safely and adequately. The authors have avoided a common fault in early books on this subject—that of confining efforts to control of spread of infection and, thus, having limited space to describe the nursing needs of sick human beings.

There can be no disagreement with the authors about their emphasis upon sound basic principles of control of spread of each disease. Details of procedures in carrying out these principles may vary among institutions and among leaders in this field, as demonstrated in the chapter on tuberculosis. Main points of nursing, such as isolation and terminal disinfection, are clearly designated for quick reference. In most instances there is emphasis on prevention of disease, although the nurse's role in this might have received more attention. Perhaps, inclusion of this material in each chapter would have made the book unwieldy and have detracted from its usefulness as a practical guide to those taking care of patients ill with the acute stages of communicable diseases.

The book is printed on a good quality paper with glossy finish. It is written in a clear direct style, which should add considerably to its practical value to nurses at various

levels of preparation. It is well illustrated and includes some colored plates. Study questions are provided at the end of each chapter and there is a useful glossary and a well-prepared index.

KATHLEEN NEWTON
New York, New York

BOOKS RECEIVED

MEDICAL PROGRESS 1954. A Review of Medical Advances During 1953. Edited by Morris Fishbein. Pp. 345, The Blakiston Company, Inc., New York, 1954, Price, $5.00.

THORACIC SURGERY. Second Edition. By Richard H. Sweet. Pp. 381, with illustrations, W. B. Saunders Company, Philadelphia and London, 1954, Price, $10.00.

MANUEL DE VACCINATION PAR LE B. C. G. By R. Mande. Pp. 200, with illustrations, Masson et Cie, Paris, 1954.

A STUDY OF THE TUBERCULOUS AT HOME IN LOS ANGELES COUNTY ON JULY 1, 1952. Los Angeles County Tuberculosis and Health Association, 1953.

Report of the Committee on Therapy to the Committee on Medical Research

The Committee on Therapy of the American Trudeau Society met in St. Louis, Missouri, on February 6, 1954. Present at the meeting were: Dr. Robert H. Ebert, chairman, and Dr. Paul Chapman, Dr. Raymond F. Corpe, Dr. Robert A. Goodwin, Jr., Dr. Roger S. Mitchell, Dr. Carl Muschenheim, Dr. Morris C. Thomas, and Dr. Robert L. Yeager. Unable to attend the meeting was Dr. Edward F. Parker.

Dr. Donald S. King, president of the American Trudeau Society, was present as a guest.

Those present from the executive office were: Dr. Floyd M. Feldmann, Dr. Esmond R. Long, Miss Agnes Fahy, Mr. Frank Webster, and Miss Rose Ashrawy.

Manual on the Pembine-type Conferences

Dr. Morris Thomas presented the final revision on the manual, which was accepted with one suggestion for revision.

Dr. Mitchell thought that parts *III. Planning a Conference* and *IV. Conference Facilities and Arrangements* would be more useful if the various points were separated under specific headings.

It was agreed that a short summary of approximately 400 words should appear in THE AMERICAN REVIEW OF TUBERCULOSIS as a statement from the ATS Committee on Therapy stating that the manual was available to persons interested in organizing Pembine-type conferences. It was also suggested that the summary statement be published in the *NTA Bulletin*. It was decided to have the manual mimeographed so that it could be sent out from the central office to groups interested in planning such conferences. Dr. Long suggested that a note might be made in *Diagnostic Standards* stating that such a manual was available.

Tuberculous Adenitis

Dr. Muschenheim presented a comprehensive review of the ancient and recent literature on the subject of tuberculous adenitis. Members of the committee then presented summary reports of their own experience with this form of tuberculosis and Dr. Goodwin gave a resumé of the Veterans Administration experience as he had been able to assemble it. There were certain general areas of agreement, and these were the necessity of prolonged chemotherapy and the fact that tuberculous adenitis was a manifestation of generalized tuberculosis and not a separate entity. Here agreement ended and considerable difference of opinion existed in the literature as well as in the personal experiences of the members of the committee about the magnitude of the problem and the best form of therapy. It was suggested that Dr. Muschenheim prepare a statement from the Committee on Therapy presenting the problem and asking for a pool of the experiences of other persons working in this field. It was believed that this would be a good preparation for a panel discussion of the problem at the meeting of the ATS in 1955.

Tuberculous Meningitis

Dr. Chapman presented a comprehensive statement on the therapy of tuberculous meningitis, and after a number of suggestions he was asked to prepare a final statement for the next meeting of the committee in May.

Tuberculosis of the Eye

Dr. Mitchell presented his review of the literature on the subject and found that there was little material in the English and American literature. Most of the articles were in Polish, Russian, Hungarian, and Czechoslavakian. After a general discussion, Dr. Mitchell was asked to write letters to the leading ophthalmology journals and the Army Pathology Museum requesting information on this subject and suggesting that a seminar on tuberculosis of the eye be prepared for the 1955 annual meeting of the ATS.

Bed Rest and Chemotherapy

Dr. Yeager presented an excellent statement entitled "Bed Rest in the Treatment of Tuberculosis." Doctors Mitchell, King, and Ebert thought that the term "relatively complete bed rest" was not precisely defined. They also believed that this portion of the statement was relatively dogmatic and not individualized enough for the particular patient; however, in general, it was unanimously believed that this was a good expression of the problem and it was decided to ask the editor of THE AMERICAN REVIEW OF TUBERCULOSIS to publish this statement in the near future.

Surgery of Tuberculosis

Dr. Corpe presented a comprehensive statement on the problems of evaluating both collapse and resectional surgery today. He was asked to prepare a briefer statement for presentation to the committee at its next meeting.

ROBERT L. YEAGER PAUL T. CHAPMAN
ROBERT A. GOODWIN MORRIS C. THOMAS
EDWARD F. PARKER ROGER MITCHELL
CARL MUSCHENHEIM RAYMOND F. CORPE
ROBERT H. EBERT, *Chairman*
Committee on Therapy

Bed Rest in the Treatment of Tuberculosis

A Statement by the Committee on Therapy

The continuing reports showing the increased effectiveness of antimicrobial therapy in the treatment of pulmonary tuberculosis have caused many physicians to question the necessity or advisability of prolonged bed rest.

This has been further accentuated by the featured publication in newspapers and magazines of proposed clinical studies, although no such studies have in fact progressed to a stage which permits even preliminary conclusions to be drawn. Programs for the treatment of unhospitalized patients are frequently misnamed and misinterpreted as "ambulatory" treatment programs, as opposed to bed-care programs. In actuality, such programs are designed to supplement hospital care of patients, rather than to replace it by: (*1*) commencing antimicrobial therapy before hospitalization can be effected in communities where there is shortage of hospitals beds; and, (*2*) continuing long-term drug therapy after control of the disease has been effected by hospital treatment. Even when home care is substituted entirely for hospital care by organized outpatient services, provision is made for bed care in the home. The designation of programs of this type as "ambulatory" presupposes an abandonment of the principle of rest therapy which is not intended and is not yet, at least, recommended by any official group.

The Committee again states that, from the facts now available, there is no evidence to support a reduction in the amount of rest therapy from that of past practices except as this may be justified by an earlier attainment of an inactive status of the disease. There

appears to be no doubt that antimicrobial therapy has materially shortened the period of recovery in the average case of tuberculosis, and that it has greatly decreased the case mortality rate. This does not necessarily imply, however, that it has altered the indications for rest therapy during the active phases of the illness.

The studies which are in progress to determine to what extent bed rest may be safely dispensed with, or in what categories or stages of the disease it may play an unimportant role in therapy, will require a long period of study. Until these studies are completed, the clinician will be well advised to adhere to the established indications for bed care. Essentially, these consist of relatively complete bed rest in accordance with previously accepted principles, until all symptoms have cleared, all cavities have been lost to view roentgenographically, all regressive infiltrations have reached an unchanging status, and sputum or gastric washings have become negative for tubercle bacilli by direct examination and culture. From this stage, gradual physical rehabilitation by progressive mobilization of the patient is permitted and is usually so graded to restore him to relatively normal activities no sooner than in six to twelve months. The total period of disability, although greatly shortened on the average, must still be estimated even in relatively mild and favorably responding cases as a minimum of one year. Even after this, the usual protective restrictions as to character and hours of work and the avoidance of strenuous exertion or fatigue must be observed for at least several years. The continuation of antimicrobial therapy itself for a total of one and one-half to two years is commonly recommended, but information is not yet available with respect to whether this provides adequate protection to permit any shortening of the convalescent period.

The indications for rest therapy during the active phases of tuberculosis are not altered by the proposals that patients may subsequently be treated with either surgical collapse or resection. A preliminary period of bed rest, combined with antimicrobial therapy, until all symptoms have cleared, cavities have diminished in size, or remain unchanged, and infiltrations have reached a relatively unchanging status is suggested. A continued period of rest after the surgical therapy is completed until it is evident that sputum or gastric washings will become and remain negative by culture and that the patient be symptom free should be used. From this stage, gradual physical rehabilitation for a period of several months, with the usual further protective restrictions, is indicated.

Robert L. Yeager — Paul T. Chapman
Robert A. Goodwin — Morris C. Thomas
Edward F. Parker — Roger Mitchell
Carl Muschenheim — Raymond F. Corpe
Robert H. Ebert, *Chairman*
Committee on Therapy

NOTES

TUBERCULOSIS SHORT COURSE FOR HEALTH OFFICERS

A short course for health officers in tuberculosis was conducted in Atlanta, Georgia, during the week of March 29 through April 1. This meeting was arranged with the cooperation of the state health departments of Georgia and Florida, Public Health Service Region IV, Atlanta, the Division of Chronic Diseases and Tuberculosis, and the Communicable Disease Center, Atlanta. Ten health officers from Florida and eight from Georgia attended the meeting.

During the meeting the problems of the two states in tuberculosis control were given thorough discussion. An interesting outcome of the meeting was the development of a resolution signed by eighteen health officers and addressed to the State Health Commissioners of Georgia and Florida. The resolution adopted was:

> Tuberculosis continues to be the number one cause of serious illness from communicable disease. We have seen an ever-increasing case load in tuberculosis and the seriousness of the problem is best measured by case rate and prevalence instead of mortality rate. In consequence, it is the consensus of this group that all services of case finding, diagnosis, case holding, treatment, financial aid and case work and rehabilitation (including vocational rehabilitation) be expanded instead of curtailed and that the public be so informed of these facts.

GRANTS TO PROMOTE FURTHER RESEARCH IN TUBERCULOSIS

The Lasdon Foundation, a philanthropic organization devoted to scientific research, has granted $10,000 to scientists at The George Washington University to promote further research in tuberculosis.

The grant will be used for laboratory and clinical studies, which are being carried on at the District of Columbia General Hospital, to investigate the best means of using available and new drugs in the treatment of tuberculosis. One phase of the research is to find a means of maintaining long-term treatment by preventing the tuberculosis bacteria from developing resistance to the drugs used for treatment.

The research will be carried on under the direction of Dr. Monroe J. Romansky, associate professor of medicine at the University, and Dr. Sol Katz, adjunct clinical professor of medicine.

Support for this project was first given by the Lasdon Foundation in 1952.

DEDICATION OF INSTITUTE OF MICROBIOLOGY, RUTGERS UNIVERSITY

Rutgers University formally dedicated its new Institute of Microbiology at New Brunswick, New Jersey, on June 7. The program featured addresses by Dr. A. J. Kluyver of the Technical University in Delft, Holland; President Lewis Webster Jones of Rutgers; and Dr. Selman A. Waksman, director of the Institute.

The Institute building, constructed during a three-year period at a cost of $3,500,000 with funds derived from royalties on streptomycin, is located on the University Heights campus, where the State University of New Jersey is developing its new science center.

The new Institute will be under the direction of Dr. Waksman, who was awarded the 1952 Nobel Prize in Physiology and Medicine for his work on antibiotics which led to the discovery of streptomycin, the first chemotherapeutic agent found to be effective against tuberculosis.

A symposium was held on June 8 and 9, which was composed of three sessions.

Dr. René J. Dubos of the Rockefeller Institute for Medical Research served as chairman of the session entitled, "The Microbe as a Living System." Speakers included Dr. C. B. van Niel of the Hopkins Marine Station, Stanford University, Dr. Andre Lwoff of the Pasteur Institute, Dr. Joshua Lederberg of the University of Wisconsin, and Dr. Bernard D. Davis of the Public Health Service.

Dr. Frits Lipmann of the Massachusetts General Hospital served as chairman of the session entitled, "Metabolism of Microorganisms." Speakers included Dr. H. Albert Barker of the University of California, Dr. W. W. Umbreit of the Merck Institute for Therapeutic Research, Dr. Jackson Foster of the University of Texas, Dr. Perry Wilson of the University of Wisconsin, and Dr. D. H. Peterson of the Upjohn Company.

Professor George W. Beadle of the California Institute of Technology served as chairman of the session entitled, "Microorganisms and Higher Forms of Life." Speakers included Professor Heidelberger of Columbia University, Dr. Frank L. Horsfall, Jr., of the Rockefeller Institute for Medical Research, Dr. Harry Eagle of the National Institutes of Health, Professor W. H. Schopfer of the University of Berne, Switzerland, and Professor Robert L. Starkey of Rutgers University.

GRANTS TO THE NATIONAL COMMITTEE FOR CAREERS IN MEDICAL TECHNOLOGY

Grants of $30,000 from the American Cancer Society and $15,000 from the National Cancer Institute of the Public Health Service were received recently by the National Committee for Careers in Medical Technology to be used in a program to recruit more young people into the profession of medical technology.

The announcement of the awards was made by the newly formed Committee, which is sponsored by the American Society of Medical Technologists, the American Society of Clinical Pathologists, and the College of American Pathologists.

Members of the NCCMT are: Dr. William O. Russell, chairman, representing the American Society of Clinical Pathologists; Miss Ruth Hovde, incoming president of the American Society of Medical Technologists; and Dr. Joseph A. Cunningham, of the College of American Pathologists. Headquarters of the Committee are in the American Council on Education Building in Washington, D. C., and Miss Dallas Johnson is Executive Secretary.

Advisers are Dr. Lall G. Montgomery, of the Board of Registry of Medical Technologists of the ASCP, and Dr. Melvin Oosting, of the Board of Schools of Medical Technology.

Although nearly 20,000 medical technologists are registered with the Board of Registry, according to Dr. Russell, the Board estimates that a total of 70,000 could be used in all phases of medical scientific work in the United States.

The Board has reported that, whereas the supply of medical technologists in this country has increased at a rate that has followed roughly the population growth, the need for the professional laboratory worker has tripled. The increased need stems from the growing number of general hospitals, public health laboratories, clinical laboratories, and from stepped-up research activities in industry and in research institutions and universities.

The American Cancer Society grant will be used to produce a twenty-minute color movie for classrooms and group meetings and a thirteen-minute black and white film for television. The National Cancer Institute grant will buy prints of the films for use by schools and educational guidance groups, science and other clubs, rural audiences such as the 4-H Clubs, and television outlets.

Churchill-Wexler of Los Angeles has been engaged by the National Committee to produce the films. The premiere showing of the color movie will be held next September in Washington, D. C., at the first American meeting of the International Congress of Clinical Pathology.

SECOND ARGENTINE CONGRESS OF THORACIC SURGERY

The Argentine Society of Thoracic Surgery, sponsored by the Chair of Thoracic Surgery of the Faculty of Medical Sciences of the University of Buenos Aires, will organize on August 17–20, 1954, the Second Argentine Congress of Thoracic Surgery and the Seventh Argentine Meeting of Thoracic Surgery.

As in previous years, this Congress intends to gather scientific personalities from all parts of the world in order to exchange ideas, opinions, and thus arrive at conclusions which will contribute to the progress of the specialty.

Persons who are interested may ask for preliminary programs, travel and hotel accommodations, and registration to the Secretaría del Congreso, Caseros 2153, Buenos Aires.

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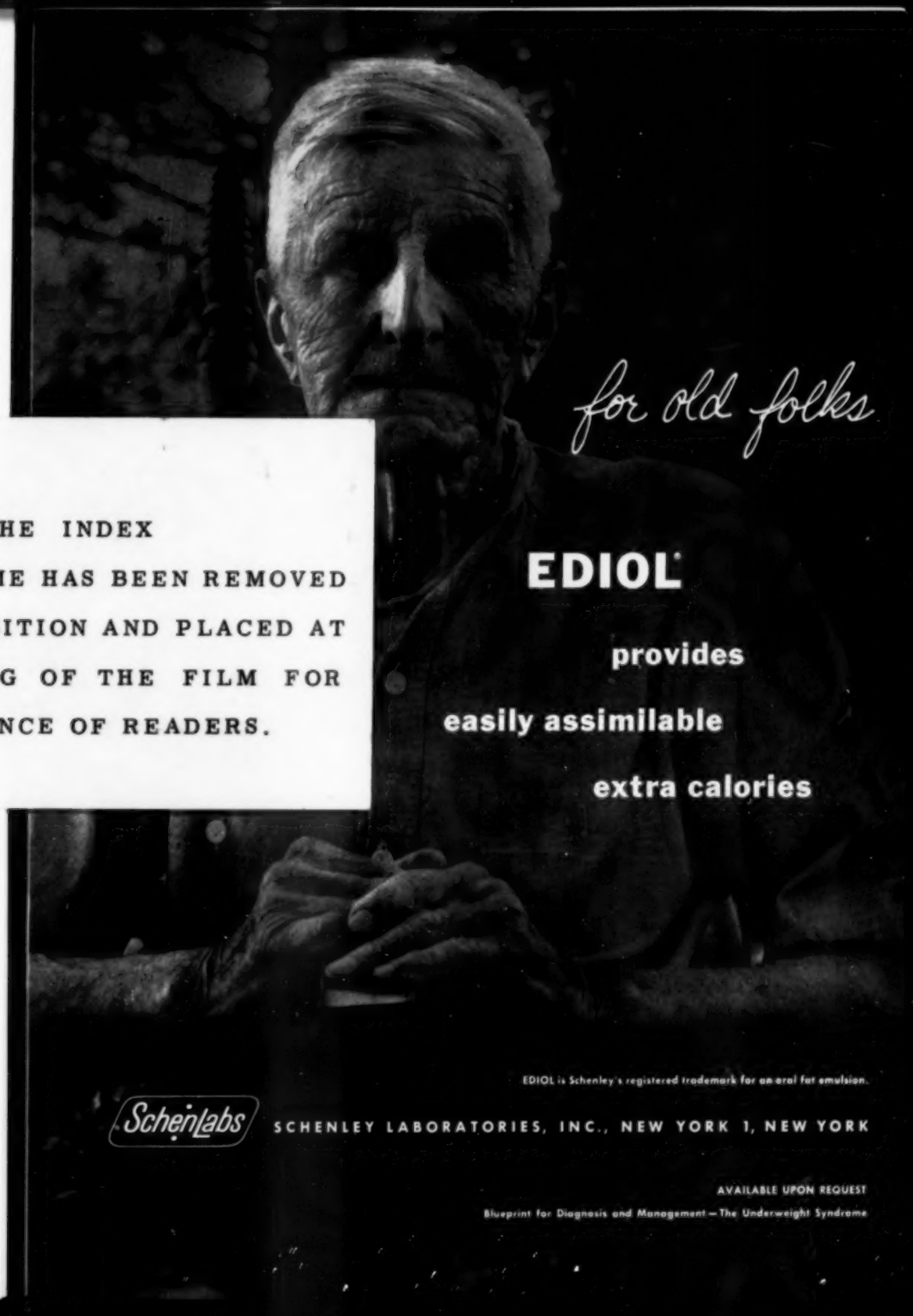

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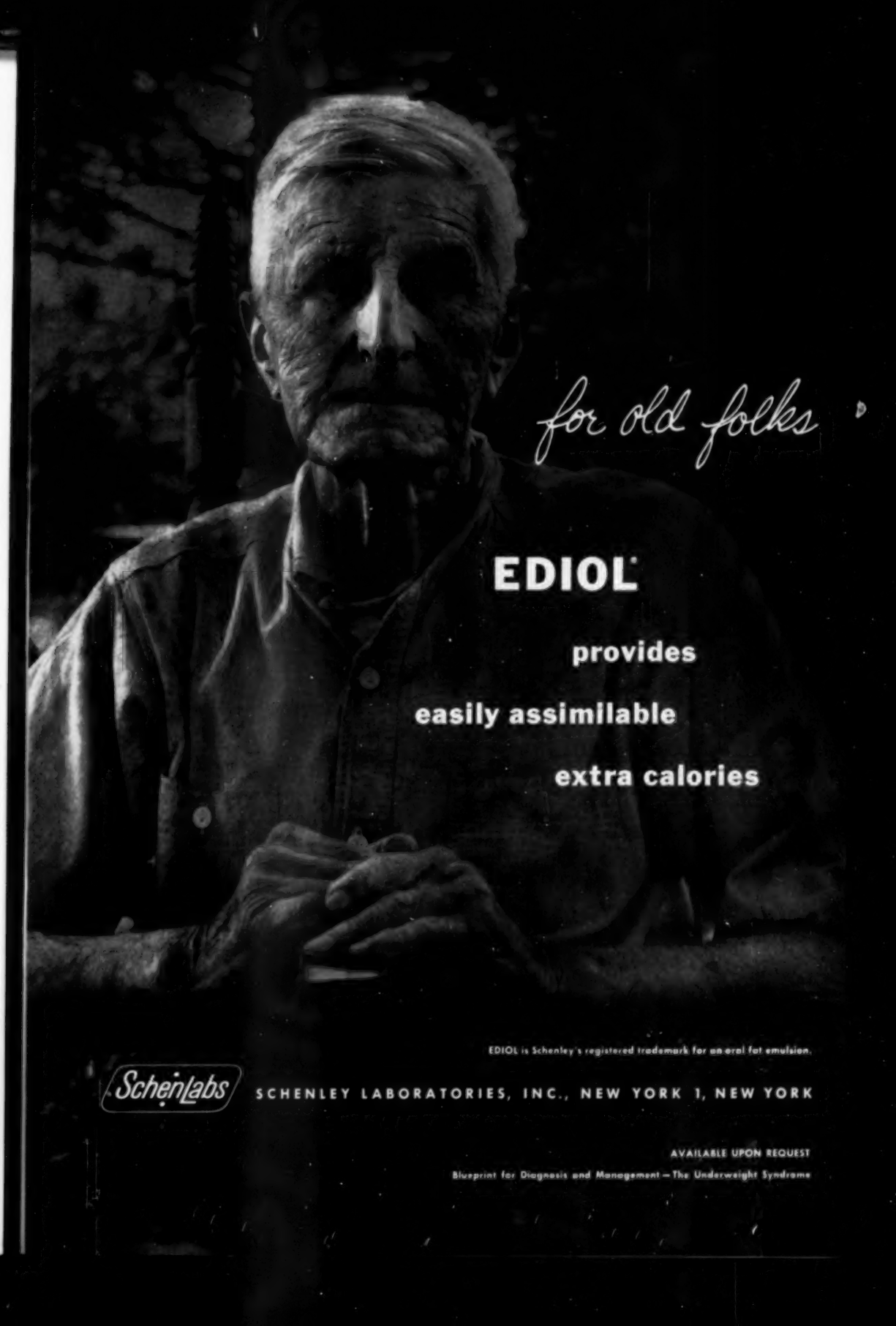

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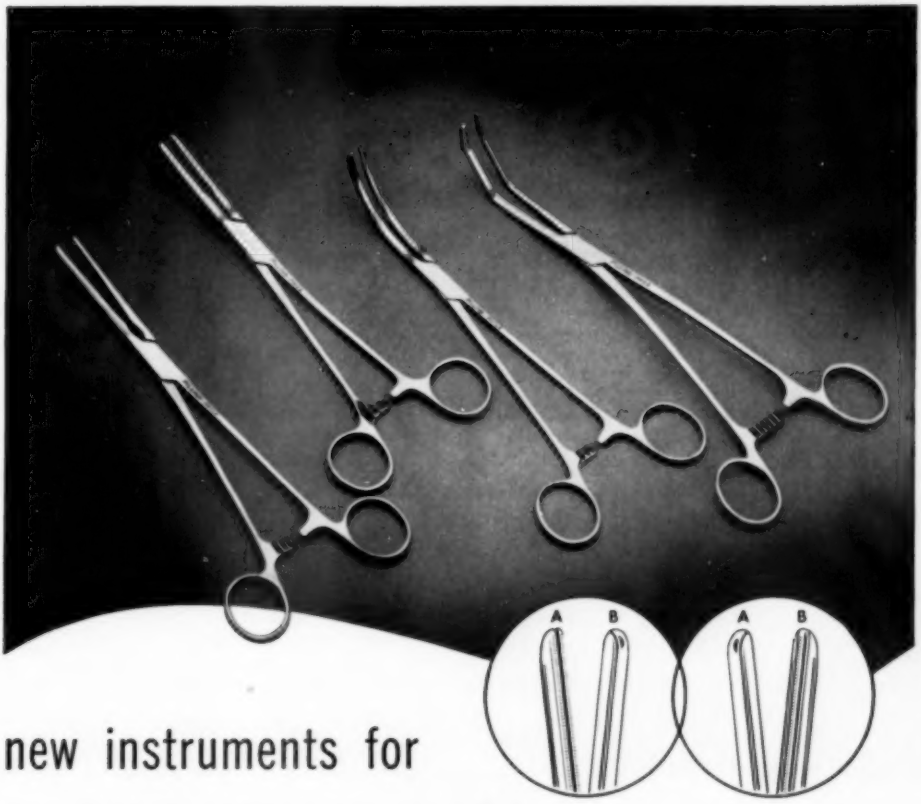

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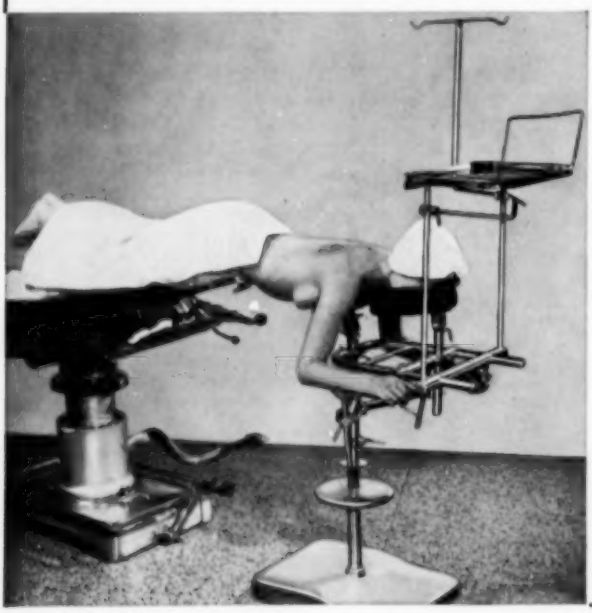

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